(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 599 543 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **93309195.1**

(51) Int. Cl.[5] : **A61K 9/107**, A61K 9/14

(22) Date of filing : **18.11.93**

(30) Priority : **19.11.92 JP 310621/92**

(43) Date of publication of application :
01.06.94 Bulletin 94/22

(84) Designated Contracting States :
DE FR GB IT

(71) Applicant : **TANABE SEIYAKU CO., LTD.**
2-10, Dosho-machi 3-chome
Chuo-ku Osaka (JP)

(72) Inventor : **Matsuda, Saburo, No. 665,**
Shogyojicho
Nijyo-dori Nishinotoin,
Higashi-iru,
Nakagyo-ku
Kyoto-shi, Kyoto-fu (JP)
Inventor : **Ishikawa, Shigeyuki**
No. 3-29, Hanjo 4-chome
Mino-shi, Osaka-fu (JP)
Inventor : **Suzuki, Akira**
No. 4-12-101, Funahara 1-chome
Itami-shi, Hyogo-ken (JP)
Inventor : **Tsujihara, Kenji**
No. 1149-133, Oaza Omaki
Urawa-shi, Saitama-ken (JP)
Inventor : **Ohashi, Motoaki**
No. 2813-2, Ankoryo Negishi
Kawaguchi-shi, Saitama-ken (JP)

(74) Representative : **Hardisty, David Robert et al**
BOULT, WADE & TENNANT
27 Furnival Street
London EC4A IPQ (GB)

(54) Pharmaceutical preparation comprising fat emulsion of fat microparticles.

(57) A preparation comprising a fat emulsion of fat microparticles wherein said emulsion contains a stabilizer consisting essentially of a fatty acid, a basic amino acid and a saccharide is provided. In the preparation comprising a fat emulsion of fat microparticles of the present invention, said microparticles having a mean particle diameter of at most 100 nm are stable, and so the microparticles remain in blood without being uptaken by liver. Therefore in case of administering a pharmaceutical preparation prepared by using the above-mentioned preparation of the present invention, the pharmacological activity may be expressed at a desired site. Thus the preparation is extremely useful as a drug carrier for drug delivery system. Furthermore, the pharmaceutical preparation of the present invention which is lyophilized can be easily and rapidly reconstituted into the pharmaceutical preparation comprising a fat emulsion of stable fat microparticles having a mean particle diameter of about at most 100 nm by adding distilled water, even after a long-term storage.

EP 0 599 543 A1

The present invention relates to a pharmaceutical preparation comprising a fat emulsion of fat microparticles.

In recent years there have been attempted to use, as a drug carrier for a fat-soluble medicinal compound, fat particles in fat emulsion which has been therapeutically employed as a neutritional support for patients after operation. In conventional fat emulsion for supplying nutrition, however, even relatively small fat particles have a mean particle diameter of as large as 200 nm. When fat particles having such a large particle diameter are used for a pharmaceutical preparation comprising fat particles containing a medicinal compound, the nharmaceutical preparation is, when administered, mostly taken up by the reticuloendothelial system such as liver and spleen, and therefore, the medicinal compound cannot be delivered to a desired site. So, it has been attempted to use fat microparticles so that they may not be taken up by the reticuloendothelial system and the medicinal compound may be delivered to the desired site. As such pharmaceutical preparation comprising a fat emulsion of fat microparticles, there have been known, for example, a fat emulsion of fat microparticles having a mean particle diameter of 40 nm to 70 nm which contain a benzo[a]phenazine anticancer drug (Japanese Unexamined Patent Publication No. 143834/1989) and a fat emulsion of fat microparticles having a mean particle diameter of 10 nm to 40 nm which contain a fat-soluble medicinal compound (Japanese Unexamined Patent Publication No. 249716/1989).

However, in a system containing microparticles, their particle diameter tends to increase with a lapse of time owing to the flocculation or coalescence thereof. Therefore, it has been difficult to obtain a long-term stable pharmaceutical preparation comprising a fat emulsion of fat microparticles.

From the viewpoint of handling, transportation and storage in a practical use of a pharmaceutical preparation, a pharmaceutical preparation comprising a fat emulsion of fat microparticles which can be stored usually as the lyophilized pharmaceutical preparation and can be easily reconstituted into the pharmaceutical preparation comprising a fat emulsion of stable fat microparticles by adding a solvent such as distilled water for injection before using, will be extremely advantageous. However, it has been very difficult to obtain such a pharmaceutical preparation.

An object of the invention is to provide a pharmaceutical preparation comprising a fat emulsion of fat micropaticles, which can be usually stored for a long period as a lyophilized product and can be easily reconstituted into the pharmaceutical preparation comprising a fat emulsion of stable fat microparticles by adding a solvent such as water, by which pharmaceutical preparation, a medicinal compound can be retained in blood without being taken up by the reticuloendothelial system.

It has been found that a pharmaceutical preparation comprising a fat emulsion of fat microparticles, which is prepared by using a stabilizer consisting essentially of a fatty acid, a basic amino acid and a saccharide, is stable for a long period, and that a lyophilized product thereof can be easily reconstituted into the pharmaceutical preparation comprising an emulsion of fat microparticles by adding aqueous solvent, such as water or saline and shaking before using.

In accordance with the present invention, there is provided a preparation as a drug carrier comprising fat emulsion of fat microparticles, wherein said emulsion contains a stabilizer consisting essentially of a fatty acid, a basic amino acid and a saccharide.

According to the present invention, there is also provided a pharmaceutical preparation comprising a fat emulsion of fat microparticles containing a fat-soluble medicinal compound wherein said emulsion contains a stabilizer consisting essentially of a fatty acid, a basic amino acid and saccharide.

Because in the pharmaceutical preparation of the present invention, fat microparticles having a mean particle diameter of at most 100 nm are stable, the microparticles remain in blood without being taken up by the liver. Therefore, in case of administering a pharmaceutical preparation of the present invention, the pharmacological activity can be presented at the desired site. Thus the preparation of the present invention is extremely useful as a drug carrier for drug delivery system. Furthermore, the pharmaceutical preparation of the present invention which is lyophilized (hereinafter referred to as "lyophilized pharmaceutical preparation") can be easily and rapidly reconstituted into the pharmaceutical preparation comprising a fat emulsion of stable fat microparticles having a mean particle diameter of about at most 100 nm by adding an aqueous solvent such as distilled water or saline, even after a long-term storage.

A fat which forms microparticles is not particularly limited in the present invention, and there can be used any fat which is liquid at ordinary temperature and is administerable per tubam. Fats and oils generally used for fat emulsion are preferable.

Representative examples of the above-mentioned fat and oil are, for instance, a vegetable oil such as purified soybean oil, corn oil, rapeseed oil, peanut oil or safflower oil; a fish oil; a synthetic fat and oil such as a triglyceride of medium chain fatty acid having 8 to 10 carbon atoms (Panasate 800, Panasate 810 and Panasate 875, all of them trade name, commercially available from Nippon Oil & Fats Co., Ltd.), squalene or AZONE (trademark, commercially available from Nelson Research USA), and the like. Among these examples, puri-

fied soybean oil and a triglyceride of medium chain fatty acid are preferable.

These fats can be used alone or in an admixture thereof.

The above-mentioned fat is suitably contained in an amount of about 1 to about 50 w/v %, preferably about 5 to about 20 w/v %, in the preparation comprising a fat emulsion of fat microparticles of the present invention.

As a fatty acid which is used as one component of a stabilizer in the present invention, there can be exemplified a saturated or unsaturated fatty acid having 6 to 32 carbon atoms.

Representative examples of the above-mentioned fatty acid include caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecylic acid, lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, heptadecylic acid, stearic acid, oleic acid, nonadecanoic acid, arachic acid, linoleic acid, linolenic acid, behenic acid, lignoceric acid, cerotic acid, heptacosanoic acid, montanic acid, melissic acid, lacceric acid, elaidic acid and brassidic acid.

Among these, fatty acids having about 6 to about 21 carbon atoms such as caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecylic acid, lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, heptadecylic acid, stearic acid, oleic acid, nonadecanoic acid, arachic acid, linoleic acid, linolenic acid and behenic acid are preferable. Further, fatty acids such as oleic acid, linoleic acid, myristic acid, stearic acid, palmitic acid and behenic acid are more preferable.

These fatty acids can be used alone or suitably in an admixture thereof.

The above-mentioned fatty acid is suitably contained in an amount of about 0.01 to about 2 w/v %, preferably about 0.5 to about 1 w/v %, in the preparation comprising a fat emulsion of fat microparticles of the present invention.

As a basic amino acid which is used together with the above-mentioned fatty acid for stabilizing fat microparticles, there can be exemplified lysine, histidine, ornithine, arginine and the like.

Among these, lysine and ornithine, particularly lysine are preferable.

It is preferable that these basic amino acids have a purity usable for injection and is in a free form.

These basic amino acids can be used alone or suitably in an admixture thereof.

The above-mentioned basic amino acid is suitably contained in an amount of about 0.05 to about 1 w/v %, preferably about 0.2 to about 0.8 w/v % so as to be an equimolar with the above-mentioned fatty acid, in the preparation comprising a fat emulsion of fat microparticles of the present invention.

As a saccharide which is also used for a stabilizer together with the above-mentioned fatty acid and the basic amino acid, a monosaccharide or a disaccharide wherein two monosaccharide molecules are linked, are preferable.

Representative examples of the above-mentioned saccharide include glucose, fructose, maltose, lactose, sucrose, trehalose and the like. Among these, maltose, trehalose and sucrose are preferable.

These saccharides can be also used alone or suitably in an admixture thereof.

The above-mentioned saccharide is suitably contained in an amount of about 2 to about 30 w/v %, preferably about 5 to about 20 w/v % in the preparation comprising a fat emulsion of fat microparticles of the present invention.

As to the proportions of the components of the stabilizer, namely a fatty acid, a basic amino acid and a saccharide in the preparation of the present invention, there may be used, for example, about 0.05 to about 4 parts by weight of the basic amino acid and about 2 to about 80 parts by weight of the saccharide, preferably, about 0.1 to about 2 parts by weight of the basic amino acid and about 4 to about 60 parts by weight of the saccharide, more preferably, about 0.4 to about 1.6 parts by weight of the basic amino acid and about 10 to about 40 parts by weight of the saccharide, per part by weight of the fatty acid.

In the pharmaceutical preparation comprising a fat emulsion of fat microparticles of the present invention which further comprises a fat-soluble medicinal compound, any fat-soluble medicinal compound can be suitably used without particular limitation. For example, on the basis of distribution coefficient between water and octanol, a compound having a large distribution coefficient e.g. at least 2, is preferable. Further, a compound having a distribution coefficient of about 2 to about 6, particularly about 4 to about 6 is more preferable.

Representative examples of the above-mentioned medicinal compound are, for example, an antiinflammatory drug, a platelet aggregation inhibiting agent, a fibrinolysis-promoting agent, an antitumour agent, a fat-soluble vitamin and the like.

As specific antiinflammatory drugs, there can be exemplified steroidal antiinflammatory drugs such as a fatty acid ester of paramethasone, nonsteroidal antiinflammatory drugs such as indomethacin and a derivative thereof, and the like. As concrete antitumour agents, there can be exemplified fluorouridine derivatives such as 3',5'-O-di-n-butanoyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine, 3',5'-O-di-n-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine, 3',5'-O-di-i-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine, 3',5'-O-dipropionyl-3-n-octanoyloxymethyl-2'-deoxy-5-fluorouridine and 3',5'-O-di-n-octanoyl-3-n-butanoyloxymethyl-2'-deoxy-5-fluorouridine, and the like. As concrete fat-soluble vitamins, there

can be exemplified tocopherol acetate and the like.

The above-mentioned medicinal compound may be suitably used within a range of amount which can express its drug efficacy, according to disease to be treated and condition, age, body weight and nature of a patient to be treated. For example, in case that an antitumour agent such as a fluorouridine derivative is used as a medicinal compound, the compound may be used in an amount of about 0.01 to about 12 w/v %, preferably about 0.1 to about 6 w/v %, more preferably about 0.3 to about 4 w/v % in the pharmaceutical preparation comprising a fat emulsion of fat microparticles of the present invention.

The lyophilized pharmaceutical preparation can be obtained by lyophilizing the pharmaceutical preparation comprising a fat emulsion of fat microparticles which contains a fat-soluble medicinal compound. In the lyophilized pharmaceutical preparation of the present invention, there preferably remains about 0.1 to about 5 % W/W of water. Both forms of the pharmaceutical preparation of the present invention, namely, emulsion and lyophilized proudct thereof can be prepared according to a conventionally known process.

The process for preparing the pharmaceutical preparation of the present invention is concretely explained below.

For example, a fatty acid and, if necessary, a fat-soluble medicinal compound are added to a fat and the mixture is dissolved at room temperature or with heating. The obtained solution is added to an aqueous solvent (e.g., distilled water, silane) containing an emulsifier, a basic amino acid, a saccharide and, if necessary, a suitable auxiliary substance, followed by mixing. The obtained mixture is crudely homogenized to give a crude emulsion containing fat particles having a mean particle diameter of about 1 μm. The obtained crude emulsion was adjusted to a desired pH with an organic acid such as malic acid and then finely emulsified to give a fine emulsion containing fat microparticles having a mean particle diameter of at most 100 nm.

Alternatively, a dispersion of an emulsifier is added to a solution which is prepared by adding a fatty acid and, if necessary, a fat-soluble medicinal compound to a fat and then dissolving the obtained mixture at room temperature or with heating. The obtained mixture is crudely homogenized and then, a basic amino acid is added thereto. The pH of the obtained mixture is adjusted with an organic acid such as malic acid and the concentration thereof is suitably adjusted by adding an aqueous solvent such as distilled water for injection. After the obtained crude emulsion is further finely emulsified, a saccharide is added thereto and the concentration is adjusted to give a fine emulsion containing fat microparticles having a mean particle diameter of at most 100 nm.

The crude-homogenation can be easily carried out by using, for example, a homogenizer at room temperature or with heating. The fine-emulsification can be carried out by using, for example, a high energy homogenizer such as Gaulin type homogenizer or Nanomizer System (trade name, made by Nanomizer Inc., Japan).

On the emulsification, an emulsifier may be advantageously used as mentioned above. The emulsifier to be used is not particularly limited and there can be used any emulsifier generally usable in this technical field.

Representative examples of such emulsifier include a lecithin such as yolk lecithin or soybean lecithin, a natural phosphatide derived from an animal such as cattle or pig, a semi-synthetic phosphatide such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol or a hydrogenated compound thereof, and the like.

These emulsifiers may be used alone or in an admixture thereof.

The above-mentioned emulsifier is suitably contained in an amount of about 0.5 to about 20 w/v %, preferably about 1 to about 10 w/v % on the basis of total volume of the preparation comprising a fat emulsion of fat microparticles of the present invention.

Further, additives or auxiliary substances such as an antioxidant, an antiseptic, an isotonic agent and a buffering agent, which are pharmaceutically acceptable and generally usable in this technical field, may be used in a suitable amount.

A lyophilized pharmaceutical preparation of the present invention can be prepared by further lyophilizing thus obtained pharmaceutical preparation comprising a fat emulsion of fat microparticles according to a known conventionally method.

For example, after mechanically sterilizing thus obtained pharmaceutical preparation comprising a fat emulsion of fat microparticles, a prescribed amount thereof is poured into a vessel for lyophilization and then pre-frozen at about -40° to about -25°C for about 10 hour. Then, the first primary drying is carried out under reduced pressure at about 0° to about 10°C for about 30 hours and successively the secondary drying is carried out under reduced pressure at about 15° to about 25°C for about 10 hours, to give the lyophilized pharmaceutical preparation of the present invention.

The present invention is more specifically described and explained by means of the following Examples. It is to be understood that the present invention is not limited to the Examples, and various changes and modifications may be made in the invention without departing from the spirit and scope thereof.

Experimental Example

(1) Preparation of pharmaceutical preparation

Pharmaceutical preparation 1 (pharmaceutical preparation of the present invention)

There were sufficiently mixed 100 g of soybean oil and 5 g of oleic acid, and thereto was added 4 g of paramethasone palmitate as a fat-soluble medicinal compound. The obtained mixture was heated to about 40°C and dissolved. Thereto was added a dispersion prepared by dispersing 48 g of yolk lecithine into 450 mℓ of previously deoxidized distilled water, followed by mixing. By using a homogenizer (Ultra-turrax, trade name, made by Ika WERK, Germany), the obtained mixture was mixed with stirring at about 10000 rpm for about 10 minutes to give a crude emulsion. To thus obtained crude emulsion was added 2.6 g of L-lysine and the mixture was adjusted to pH 7.5 with malic acid. Thereto was added a suitable amount of distilled water for injection to make the total volume of 900 mℓ. After the obtained crude emulsion was allowed to stand under reduced pressure for about 10 to about 20 minutes for deaeration, it was finely emulsified under high pressure at 40°C, emulsifying pressure of 1000 kgf/cm^2 by means of a high energy homogenizer (Nanomizer System LA-11, trade name made, by Nanomizer Inc., Japan) to give a fine emulsion. Then 100 g of maltose was added to the obtained fine emulsion, and dissolved therein. The total volume thereof was made to 1000 mℓ to give a pharmaceutical preparation comprising a fat emulsion of fat microparticles.

Every about 3 mℓ of the obtained pharmaceutical preparation was put into a 10 mℓ -glass vial, and pre-frozen by means of a lyophilizing machine (Minifast 1700, trade name, made by Edwards, Great Britain) at -25°C for 6 hours. The pre-frozen pharmaceutical preparation was primarily dried under reduced pressure at 0°C for 30 hours, and further secondly dried under reduced pressure at 20°C for 8 hours to give a lyophilized pharmaceutical preparation (hereinafter, referred to as "Pharmaceutical preparation 1").

Control pharmaceutical preparation 1

In the same manner as described in the above-mentioned Pharmaceutical preparation 1 except that oleic acid and maltose were not used, there was prepared a lyophilized pharmaceutical preparation (hereinafter, referred to as "Control pharmaceutical preparation 1").

Control pharmaceutical preparation 2

In the same manner as described in the above-mentioned Pharmaceutical preparation 1 except that oleic acid was not used, there was prepared a lyophilized pharmaceutical preparation (hereinafter, referred to as "Control pharmaceutical preparation 2").

(2) Storage stability test

With respect to (i) each pharmaceutical preparation in the form of emulsion just after the fine-emulsification, (ii) each lyophilized pharmaceutical preparation thereof just after the lyophilization and (iii) each lyophilized pharmaceutical preparation after the storage at 40°C for 1 month, a mean particle diameter of fat microparticles was measured in order to examine their stability.

In the above-mentioned measurement, both lyophilized pharmaceutical preparations just after the lyophilization and after the storage for 1 month were reconstituted into emulsion for the measurement by adding 3 mℓ of distilled water for injection respectively and lightly shaking.

The mean particle diameter was measured by means of light-scattering photometer (quasi-elastic lazer light scattering particle sizer) (ELS-800 type, trade name, made by OTSUKA ELECTRONICS, Japan).

(3) Results

The results are shown in Table 1. In the pharmaceutical preparations of the present invention, the fat microparticles had a mean particle diameter of at most 100 nm and were stable at any stage, namely, just after the fine-emulsification, just after the lyophilization and after the storage with heating. On the contrary, in the control pharmaceutical preparations, not only there could not be obtained microparticles having a mean particle diameter of at most 100 nm in spite of fine-emulsification, but also it is shown that during the lyophilization or the storage, the mean particle diameter of the fat particles was further enlarged or the particles were destroyed.

Table 1

	Component of Stabilizer	Mean particle diameter of fat particles (nm)		
		Just after fine-emulsification	Just after lyophilization	After storage at 40℃ for 1 month
Present invention				
Pharmaceutical preparation 1	Oleic acid L-Lysine Maltose	88	94	98
Control				
Control pharmaceutical preparation 1	L-Lysine	141	Unmeasurable because of viscous oily state of the pharmaceutical preparation	Unmeasurable because of viscous oily state of the pharmaceutical preparation
Control pharmaceutical preparation 2	L-Lysine Maltose	145	160	190

Example 1

There were sufficiently mixed 100 g of soybean oil and 5 g of oleic acid, and thereto was added 1 g of free diltiazem as a fat-soluble medicinal compound. The obtained mixture was heated to about 40°C and dissolved. Thereto was added a dispersion prepared by dispersing 48 g of yolk lecithine into 450 mℓ of previously deoxidized distilled water, followed by mixing. By using a homogenizer (Utra-turrax), the obtained mixture was mixed with stirring at about 10000 rpm for about 10 minutes to give a crude emulsion. To thus obtained crude emulsion was added 2.6 g of L-lysine and the mixture was adjusted to pH 7.5 with malic acid. Thereto was added a suitable amount of distilled water for injection to make the total volume of 900 mℓ. After the obtained crude emulsion was allowed to stand under reduced pressure for about 10 to about 20 minutes for deaeration, it was finely emulsified under high pressure (1000 kgf/cm^2) at 40°C, by means of a high energy homogenizer (Nanomizer System LA-11, trade name) to give a fine emulsion. Then 100 g of trehalose was added to the obtained fine emulsion, and dissolved therein. The total volume thereof was made to 1000 mℓ to give a pharmaceutical preparation comprising a fat emulsion of fat microparticles.

The obtained pharmaceutical preparation was pre-frozen at -25°C for 6 hours, and lyophilized at 0°C for 30 hours, and further at 20°C for 8 hours to give a lyophilized pharmaceutical preparation comprising a fat emulsion of fat microparticles of the present invention.

When the lyophilized pharmaceutical preparation was reconstituted into a fat emulsion by adding distilled water, the mean particle diameter of fat microparticles therein was found to be about 90 nm, which was not different from that in the pharmaceutical preparation before the lyophilization.

Example 2

In the same manner as described in Example 1 except for using 100 g of triglyceride of capric acid (Panasate 800, trade name, available from Nippon Oil & Fats Co., Ltd., Japan), 5 g of oleic acid, 48 g of yolk lecithin, 2.6 g of L-lysine, 4 g of paramethasone palmitate and 100 g of maltose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 70 nm.

The obtained pharmaceutical preparation was pre-frozen at -25°C for 10 hours, and lyophilized at 0°C for 40 hours, and further at 20°C for 8 hours to give a lyophilized pharmaceutical preparation containing fat microparticles.

When the lyophilized pharmaceutical preparation was reconstituted into a fat emulsion by adding distilled water, the mean particle diameter of fat microparticles therein was found to be about 70 nm, which was not different from that in the pharmaceutical preparation before the lyophilization.

Example 3

In the same manner as described in Example 1 except for using 100 g of soybean oil, 5 of oleic acid, 48 g of yolk lecithine, 2.6 g of L-lysine, 20 g of tocopherol acetate as a fat-soluble medicinal compound and 100 g of trehalose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 100 nm.

The obtained pharmaceutical preparation was pre-frozen at -25°C for 6 hours, and lyophilized at 0°C for 30 hours and further at 20°C for 8 hours to give a lyophilized pharmaceutical preparation containing fat microparticles.

When the lyophilized pharmaceutical preparation was reconstituted into a fat emulsion by adding distilled water, the mean particle diameter of fat microparticles therein was found to be about 100 nm, which was not different from that in the pharmaceutical preparation before the lyophilization.

Example 4

In the same manner as described in Example 1 except for using 100 g of Panasate 800, 5 g of oleic acid, 48 g of yolk lecithin, 2.6 g of L-lysine, 20 g of 3', 5'-O-di-n-butanoyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine and 100 g of maltose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 90 nm.

The obtained pharmaceutical preparation was pre-frozen at -25°C for 10 hours, and lyophilized at 0°C for 40 hours and further at 20°C for 8 hours to give a lyophilized pharmaceutical preparation comprising a fat emulsion of fat microparticles of the present invention.

When the lyophilized pharmaceutical preparation was reconstituted into a fat emulsion by adding distilled water, the mean particle diameter of fat microparticles therein was found to be about 90 nm, which was not

different from that in the pharmaceutical preparation before the lyophilization.

Examples 5 to 8

In the same manner as described in Example 4 except for using each of the following medicinal compounds as a fat-soluble medicinal compound, there were prepared lyophilized pharmaceutical preparations comprising a fat emulsion of fat microparticles containing each of them.

Medicinal compound:

3',5'-O-di-n-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine
3',5'-O-di-i-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine
3',5'-O-dipropionyl-3-n-octanoyloxymethyl-2'-deoxy-5-fluorouridine
3',5'-O-di-n-octanoyl-3-n-butanoyloxymethyl-2'-deoxy-5-fluorouridine

Example 9

In the same manner as described in Example 1 except for using 100 g of a triglyceride of fatty acid (Panasate 810, trade name, composition of the fatty acid: caprylic acid/capric acid = 85/15, available from Nippon Oil & Fats Co., Ltd.), 5 g of linoleic acid, 48 g of yolk lecithin, 2.6 g of L-lysine, 20 g of 3',5'-O-di-n-butanoyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine and 10 g of sucrose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 85 nm.

The obtained pharmaceutical preparation was pre-frozen at -30°C for 8 hours, and lyophilized at 5°C for 36 hours and further at 25°C for 8 hours to give a lyophilized pharmaceutical preparation comprising a fat emulsion of fat microparticles of the present invention.

When the lyophilized pharmaceutical preparation was reconstituted into a fat emulsion by adding distilled water, the mean particle diameter of fat microparticles therein was found to be about 90 nm, which was not different from that in the pharmaceutical preparation before the lyophilization.

Example 10

In the same manner as described in Example 1 except for using 100 g of a triglyceride of fatty acid (Panasate 875, trade name, composition of the fatty acid: caprylic acid/capric acid = 75/25, available from Nippon Oil & Fats Co., Ltd.), 5 g of oleic acid, 48 g of yolk lecithin, 2.4 g of L-ornithine, 5 g of tocopherol acetate and 10 g of maltose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 80 nm.

Example 11

In the same manner as described in Example 1 except for using 100 g of Panasate 800, 5 g of linoleic acid, 48 g of yolk lecithin, 2.4 g of L-ornithine, 20 g of 3',5'-O-di-n-butanoyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine and 10 of trehalose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 90 nm.

Example 12

In the same manner as described in Example 1 except for using 100 g of soybean oil, 5 g of stearic acid, 48 g of yolk lecithin, 2.6 g of L-lysine, 20 g of 3',5'-O-di-n-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine and 10 g of maltose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 90 nm.

Example 13

In the same manner as described in Example 1 except for using 100 g of Panasate 800, 5 g of myristic acid, 48 g of yolk lecithin, 2.1 g of L-lysine, 20 g of 3',5'-O-dipropionyl-3-n-octanoyloxymethyl-2'-deoxy-5-fluorouridine and 10 g of maltose, there was prepared a pharmaceutical preparation comprising a fat emulsion of fat microparticles having a mean particle diameter of about 80 nm.

Reference Example 1

(a) To 70 mℓ of acetone was added 4.95 g of 5-fluoro-2'-deoxyuridine and 12 g of sodium iodide. With stirring at room temperature, thereto was added 7.19 g of chloromethyl n-heptanoate and 15 g of anhydrous potassium carbonate. After the mixture was reacted with stirring at room temperature overnight, the obtained mixture was concentrated under reduced pressure. To the concentrate was added 150 mℓ of ethyl acetate, and then the insoluble matter was separated by filtration. The filtrate was washed with water, saturated aqueous solution of sodium chloride and water successively, followed by concentrating. The obtained concentrate was purified by silica gel column chromatography (eluting solvent: ethyl acetate) to give 4.77 g of 3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of colorless solid matter (yield: 61.1 %). The melting point of the obtained solid matter was 104° to 106°C.

(b) Into 30 mℓ of methylene chloride was dissolved 583 mg of the colorless solid matter obtained in the above (a). With stirring under cooling with ice, thereto was added 1.05 mℓ of triethylamine and then dropwise a methylene chloride solution containing 480 mg of butanoyl chloride.

After the mixture was reacted at room temperature for 2 hours, the obtained solution was washed with cold water, cold aqueous solution of sodium bicarbonate and saturated aqueous solution of sodium chloride successively. After the solvent was distilled away, the obtained residue was purified by silica gel column chromatography (eluting solvent: ethyl acetate/n-hexane = 1/4) to give 760 mg of 3',5'-O-di-n-butanoyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of colorless oily matter (yield: 89.0 %). The solubility of the obtained oily matter in soybean oil was more than 300 mg/mℓ.

IR (Neat): ν_{max} (cm^{-1}) 1740, 1690, 1680, 1470, 1280, 1170, 1100

Reference Example 2

In the same manner as described in Reference Example 1(b) except for using 2.25 g of the product obtained in Reference Example 1(a) and 1.74 g of n-butyl chloroformate, there was prepared 2.63 g of 3',5'-O-di-n-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of colorless oily matter (yield: 77.2 %).

IR (Neat): ν_{max} (cm^{-1}) 1750, 1690, 1680, 1470, 1260

Reference Example 3

In the same manner as described in Reference Example 1(b) except for using 1.50 g of the product obtained in Reference Example 1(a), 1.19 g of i-butyl chloroformate and 30 mℓ of pyridine, there was prepared 2.63 g of 3',5'-O-di-i-butoxycarbonyl-3-n-heptanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of pale yellow oily matter (yield: 86.5 %).

IR (Neat): ν_{max} (cm^{-1}) 3095, 2960, 2875, 1748, 1695, 1680

Reference Example 4

(a) In the same manner as described in Reference Example 1(a) except for using 3 g of 5-fluoro-2'-deoxyuridine, 9.10 g of anhydrous potassium carbonate, 6.58 g of sodium iodide and 4.70 g of chloromethyl n-octanoate, there was prepared 3.17 g of 3-n-octanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of colorless crystal (yield: 64.7 %). The melting point of the obtained crystal was 74.0° to 77.9°C.

(b) In the same manner as described in Reference Example 1(b) except for using 1.50 g of the product obtained in the above (a), 1.03 g of propionyl chloride and 30 mℓ of pyridine, there was prepared 1.07 g of 3',5'-O-dipropionyl-3-n-octanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of pale yellow oily matter (yield: 55.8 %).

IR (Neat): ν_{max} (cm^{-1}) 1740, 1680

Reference Example 5

(a) In the same manner as described in Reference Example 1(a) except for using 2.2 g of 5-fluoro-2'-deoxyuridine, 6.67 g of anhydrous potassium carbonate, 4.82 g of sodium iodide and 2.44 g of chloromethyl n-butanoate, there was prepared 1.82 g of 3-n-butanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of white powder (yield: 58.9 %). The melting point of the obtained powder was 103.0° to 105.0°C.

(b) In the same manner as described in Reference Example 1(b) except for using 1.50 g of the product obtained in the above (a), 1.76 g of n-octanoyl chloride and 20 mℓ of pyridine, there was prepared 1.16 g

of 3',5'-O-di-n-octanoyl-3-n-butanoyloxymethyl-2'-deoxy-5-fluorouridine in the form of pale yellow oily matter.

IR (Neat): ν_{max} (cm^{-1}) 1740, 1681

In addition to the ingredients used in the Examples, other ingredients can be used in the Examples as set forth in the specification to obtain substantially the same results.

Claims

1. A preparation for use as a drug carrier comprising a fat emulsion of fat microparticles, wherein said emulsion contains a stabilising agent consisting essentially of a fatty acid, a basic amino acid and a saccharide.

2. A pharmaceutical preparation comprising a fat emulsion of fat microparticles containing a fat-soluble medicinal compound, wherein said emulsion contains a stabilising agent consisting essentially of a fatty acid, a basic amino acid and a saccharide.

3. A preparation as claimed in either of claims 1 and 2, wherein the fatty acid is a fatty acid having 6 to 32 carbon atoms.

4. A preparation as claimed in claim 3, wherein the fatty acid is selected from oleic acid, linoleic acid, myristic acid, stearic acid, palmitic acid and behenic acid and any mixture thereof.

5. A preparation as claimed in any one of the preceding claims, wherein the basic amino acid is selected from lysine, histidine, ornithine and arginine, and mixtures thereof.

6. A preparation as claimed in any one of the preceding claims, wherein the saccharide is a monosaccharide or a disaccharide.

7. A preparation as claimed in claim 6, wherein the saccharide is selected from glucose, fructose, maltose, lactose, sucrose and trehalose, and mixtures thereof.

8. A preparation as claimed in claim 6, wherein the saccharide is maltose or trahalose.

9. A preparation as claimed in either of claims 1 and 2, wherein the fatty acid is oleic acid, the basic amino acid is lysine and the saccharide is maltose or trehalose.

10. A preparation as claimed in any one of the preceding claims, wherein the fat microparticles have a mean particle diameter of at most 100 nm.

11. A preparation as claimed in any one of the preceding claims, which comprises about 0.05 to about 4 parts by weight of the basis amino acid, about 2 to about 80 parts by weight of the saccharide per part by weight of the fatty acid.

12. A pharmaceutical preparation as claimed in any one of claims 2 to 11 in lyophized form.

13. The use of a stabilising agent consisting essentially of or comprising a fatty acid, a basic amino acid and a saccharide as defined in any one of the preceding claims in the stabilisation of an emulsion of fat particles.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 9195

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X,Y	EP-A-0 331 755 (TEIJIN LIMITED) * claims 1-4,6 * * page 4, line 49 - page 5, line 15 * * page 5, line 58 - page 6, line 4 * * page 6, line 27 - line 41 *	1-7,13	A61K9/107 A61K9/14
X	EP-A-0 325 244 (EISAI CO. LTD.) * page 2, line 1 - line 3 * * page 2, line 25 - line 30 * * example 1 *	1-3,5-7, 11,13	
Y	EP-A-0 355 604 (LEDERLE (JAPAN) LTD.) * claims 1,5 * * page 4, line 56 - page 5, line 9 * * page 5, line 40 - line 53 *	1-7,13	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 January 1994	Ventura Amat, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 260 219 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
27.11.2002 Bulletin 2002/48

(51) Int Cl.7: **A61K 9/38**

(21) Application number: **02253342.6**

(22) Date of filing: **14.05.2002**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **15.05.2001 US 291127 P**
28.09.2001 US 325726 P
12.04.2002 US 122999

(71) Applicant: **McNeil-PPC, Inc.**
Skillman, NJ 08558-9418 (US)

(72) Inventors:
- **Gulian, Cynthia**
  Lansdale, PA 19446 (US)
- **Gowan, Walter G. Jr.**
  Woodstock, GA 30189 (US)
- **Parekh, Kishor B.**
  Horsham, PA 19044 (US)
- **Morris, Joseph M.**
  Coatesville, PA 19320 (US)
- **Markley, Thomas J.**
  North Wales, PA 19454 (US)
- **Wieand, Dennis C**
  Coopersburg, PA 18036 (US)
- **McNally, Gerard P.**
  Berwyn, PA 19312 (US)

(74) Representative: **Mercer, Christopher Paul et al**
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

(54) Dip coating compositions containing cellulose ethers

(57) Water soluble, gelatin-free dip coatings for pharmaceutical solid dosage forms such as tablets comprising HPMC and xanthan gum, carrageenan, and mixtures thereof, or HPMC and castor oil or maltodextrin.

EP 1 260 219 A2

Description

FIELD OF THE INVENTION

[0001] This invention relates to novel, water soluble, gelatin-free compositions for dip coating substrates, such as tablets and capsules, and methods for producing such dosage forms. This invention further relates to a method for increasing the weight gain of a water soluble, gelatin-free, film forming coating on a dip-coated tablet or caplet.

BACKGROUND OF THE INVENTION

[0002] During most of this century, hard gelatin capsules were a popular dosage form for prescription and over-the-counter (OTC) drugs. The ability to combine capsule halves having different colors provided manufacturers with a unique means of distinguishing various pharmaceutical products. Many patients preferred capsules over tablets, perceiving them as being easier to swallow. This consumer preference prompted pharmaceutical manufacturers to market certain products in capsule form even when they were also available in tablet form.

[0003] Generally, empty hard gelatin capsules are manufactured using automated equipment. This equipment employs rows of stainless steel pins, mounted on bars or plates, which are dipped into a gelatin solution maintained at a uniform temperature and fluidity. The pins are then withdrawn from the gelatin solution, rotated, and then inserted into drying kilns through which a strong blast of filtered air with controlled humidity is forced. A crude capsule half is thus formed over each pin during drying. Each capsule half is then stripped, trimmed to uniform length, filled and joined to an appropriate mating half.

[0004] An alternative to capsule products are caplets, which are solid, oblong tablets that are often coated with various polymers such as cellulose ethers to improve their aesthetics, stability, and swallowability. Typically, such polymers are applied to the tablets either from solution in organic solvents, or from aqueous dispersion via spraying. However, such spray-coated tablets lack the shiny surface and elegance of the hard gelatin capsules. Additionally, it is not commercially feasible to spray-coat a tablet with a different color coating on each end.

[0005] Another alternative to capsule products are "gelcaps," which are elegant, shiny, consumer-preferred dosage forms that are prepared by dipping each half of an elongated tablet in two different colors of gelatin solution. See United States Patent Nos.: 4,820,524; 5,538,125; 5,685,589; 5,770,225; 5,198,227; and 5,296,233, which are all incorporated by reference herein. A similar dosage form, commercially available as a "geltab," is prepared by dipping each half of a round, convex tablet into different colors of gelatin solution, as described in United States Patent Nos. 5,228,916, US5,436,026 and US5,679,406, which are all incorporated by reference herein. As used herein, such "gelcaps" and "geltabs" shall be included within the broader term, "tablets."

[0006] However, the use of gelatin as a pharmaceutical coating material presents certain disadvantages and limitations, including the potential for decreased dissolution rate after extended storage due to cross-linking of the gelatin, potential for microbial contamination of the gelatin solution during processing, and long processing times due to extensive drying requirements. Further, the energy-related costs associated with gelatin coatings tend to be high since the gelatin material is typically applied to the substrates at an elevated temperature of at least about 40°C in order to maintain fluidity of the gelatin, while the substrates are maintained at about 50°C in order to minimize microbial growth.

[0007] Various attempts have been made to produce gelatin-free hard shell capsules. For example, WO 00/18835 discloses the combination of starch ethers or oxidized starch and hydrocolloids for use in preparing hard capsule shells via conventional dip molding processing. See also U.S. Pat. No. 4,001211 (capsules prepared via pin dip coating with thermogelled methylcellulose ether compositions). However, due to potential tampering concerns, hard gelatin capsules are no longer a preferred delivery system for consumer (over-the-counter) pharmaceuticals, dietary supplements, or other such products. Additionally, the properties of an ideal composition into which steel pins are to be dipped then dried to form hard capsule shells thereon are not necessarily the same as those for dipping tablets to form a coating thereon. For example, relevant physical properties such as viscosity, weight-gain, film thickness, tensile strength, elasticity, and moisture content will differ between compositions for hard capsule formation and for coating tablets. See e. g., U.S. Pat. No. 1,787,777 (Optimal temperatures of the substrate and coating solution, residence times in the solution, and drying conditions differ.)

[0008] One disadvantage associated with dipping tablets or capsules into a non-gelatin coating system is that the resulting coatings often lack adequate tensile strength, plasticity, hardness, and thickness. Moreover, the inclusion of plasticizers into such non-gelatin coating systems often results in tablets having soft, tacky coatings without a hardness sufficient to maintain their shape or smoothness during handling. In addition, many non-gelatin compositions do not adhere to the tablet substrate in an amount sufficient to uniformly cover the tablet after a single dipping. Further, many non-gelatin compositions lack the sufficient rheological properties necessary to maintain uniform color dispersion throughout the dipping and drying process. Although attempts have been made to improve the rheological properties of these compositions by, for example, increasing their solids content in order to increase viscosity. However, such

compositions often disadvantageously resulted in undesirable coating aesthetics such as surface roughness, decreased gloss, and non-uniform coating thickness.

[0009] It is desirable to find a dip coating material, which not only produces a similar elegant, shiny, high gloss, consumer-preferred dosage form similar to that of gelatin-coated forms, but which is absent the limitations of gelatin, particularly those noted above.

SUMMARY OF THE INVENTION

[0010] The present invention provides for a film forming composition for dip coating a substrate comprising, consisting of, and/or consisting essentially of:

a) hydroxypropylmethyl cellulose; and
b) a thickener selected from the group consisting of xanthan gum, carrageenan, and mixtures thereof,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

[0011] Another embodiment of the present invention is directed to a water soluble composition for dip-coating a substrate comprising, consisting of, and/or consisting essentially of:

a) hydroxypropylmethyl cellulose; and
b) castor oil,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

[0012] Another embodiment of the present invention is directed to a water soluble composition for dip-coating a substrate comprising, consisting of, and/or consisting essentially of:

a) hydroxypropylmethyl cellulose; and
b) maltodextrin,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

[0013] We have found that when a dosage form is coated with the composition of the present invention, the result is an elegant, shiny, high gloss, consumer-preferred dosage form similar to that of a gelatin-coated form, but which lacks the limitations associated with gelatin, particularly those noted above. We have also found that when such a composition is used in dip coating and spray coating operations, it does not inhibit the dissolution of the active coated therewith. Further, we have found that the color uniformity of dosage forms coated with such compositions is improved upon the addition of a weight gain enhancer thereto.

DETAILED DESCRIPTION OF THE INVENTION

[0014] As used herein, "capsules" refer to hard shell compartments that enclose a dosable ingredient. "Tablets," as used herein, refer to compressed or molded solid dosage forms of any shape or size. "Caplets," as used herein, refer to solid, oblong-shaped tablets. "Gelcaps" refer to solid caplets having a glossy gelatinous coating, and "geltabs" refer to solid tablets having flat sides, convex opposing faces, and a glossy gelatinous coating. "Hardness" as used herein in connection with films or coatings indicates the resistance of the film/coating to deformation upon impact. "Water soluble," as used herein in connection with non-polymeric materials, shall mean from sparingly soluble to very soluble, i.e., not more than 100 parts water required to dissolve 1 part of the non-polymeric, water soluble solute. See Remington, "The Science and Practice of Pharmacy," pages 208 - 209 (2000). "Water soluble," as used herein in connection with polymeric materials, shall mean that the polymer swells in water and can be dispersed at the molecular level to form a homogeneous dispersion or colloidal "solution." "Surface gloss" as used herein, shall refer to amount of light reflectance as measured at a 60 degree incident angle using the method set forth in Example 7 herein.

[0015] Dimethicone is a well known pharmaceutical material consisting of linear siloxane polymers containing repeating units of the formula $\{-(CH_2)_2SiO\}_n$ stabilized with trimethylsiloxy end blocking units of the formula $[(CH_3)_3SiO-]$. Simethicone is the mixture of dimethicone and silicon dioxide. For the purposes of this invention, the two materials may be used interchangably.

[0016] The first embodiment of this invention is directed to water soluble, substantially gelatin-free, film forming compositions for dip coating tablets or manufacturing capsules via a dip molding process. One composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and a thickener, such as a hydrocolloid, e.g., xanthan gum or carrageenan. In another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a modified starch selected from waxy maize

starch, tapioca dextrin, and derivatives and mixtures thereof; a thickener selected from sucrose, dextrose, fructose, maltodextrin, polydextrose, and derivatives and mixtures thereof; and a plasticizer, e.g., polyethylene glycol, propylene glycol, vegetable oils such as castor oil, glycerin, and mixtures thereof. In yet another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and optionally a plasticizer, such as vegetable oils, e.g., castor oil; and may optionally be substantially free of thickeners such as hydrocolloids, e.g. xanthan gum. In yet another embodiment, the composition comprises, consists of, and/or consists essentially of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; an extender, such as polycarbohydrates, e.g. maltodextrin; and optionally a plasticizer, such as glycols, e.g., polyethylene glycol; and may optionally be substantially free of thickeners such as hydrocolloids, e.g. xanthan gum. As used herein, "substantially gelatin-free" shall mean less than about 1 percent, e.g. less than about 0.5 percent, of gelatin in the composition, and "substantially free of thickeners" shall mean less than about 1 percent, e.g. less than about 0.01 percent, of thickeners in the composition.

[0017] Any film former known in the art is suitable for use in film forming composition of the present invention. Examples of suitable film formers include, but are not limited to, polyvinylalcohol (PVA), hydroxypropyl starch, hydroxyethyl starch, pullulan, methylethyl starch, carboxymethyl starch, methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxypropylmethylcellulose (HPMC), hydroxybutylmethylcellulose (HBMC), hydroxyethylethylcellulose (HEEC), hydroxyethylhydroxypropylmethyl cellulose (HEMPMC), pre-gelatinized starches, and polymers and derivatives and mixtures thereof.

[0018] One suitable hydroxypropylmethylcellulose compound is "HPMC 2910", which is a cellulose ether having a degree of substitution of about 1.9 and a hydroxypropyl molar substitution of 0.23, and containing, based upon the total weight of the compound, from about 29% to about 30% methoxyl and from about 7% to about 12% hydroxylpropyl groups. HPMC 2910 is commercially available from the Dow Chemical Company under the tradename, "Methocel E." "Methocel E5, " which is one grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 4 to 6 cps (4 to 6 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. Similarly, "Methocel E6 ," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 5 to 7 cps (5 to 7 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. "Methocel E15," which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 15000 cps (15 millipascal-seconds) at 20 °C in a 2% aqueous solution as determined by a Ubbelohde viscometer. As used herein, "degree of substitution" shall mean the average number of substituent groups attached to a anhydroglucose ring, and "hydroxypropyl molar substitution" shall mean the number of moles of hydroxypropyl per mole anhydroglucose.

[0019] As used herein, "modified starches" include starches that have been modified by crosslinking, chemically modified for improved stability, or physically modified for improved solubility properties. As used herein, "pre-gelatinized starches" or "instantized starches" refers to modified starches that have been pre-wetted, then dried to enhance their cold-water solubility. Suitable modified starches are commercially available from several suppliers such as, for example, A.E. Staley Manufacturing Company, and National Starch & Chemical Company. One suitable modified starch includes the pre-gelatinized waxy maize derivative starches that are commercially available from National Starch & Chemical Company under the tradenames, "Purity Gum" and "FilmSet", and derivatives, copolymers, and mixtures thereof. Such waxy maize starches typically contain, based upon the total weight of the starch, from about 0 percent to about 18 percent of amylose and from about 100 percent to about 88 percent of amylopectin.

[0020] Suitable tapioca dextrins include those available from National Starch & Chemical Company under the tradename, "Crystal Gum" or "K-4484," and derivatives thereof such as modified food starch derived from tapioca, which is available from National Starch and Chemical under the tradename, "Purity Gum 40," and copolymers and mixtures thereof.

[0021] Any thickener known in the art is suitable for use in the film forming composition of the present invention. Examples of such thickeners include but are not limited to hydrocolloids such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan, and derivatives and mixtures thereof. Additional suitable thickeners include sucrose, dextrose, fructose, maltodextrin, polydextrose, and the like, and derivatives and combinations thereof.

[0022] Suitable xanthan gums include those available from C.P. Kelco Company under the tradename, "Keltrol 1000," "Xantrol 180," or "K9B310."

[0023] Any plasticizer known in the pharmaceutical art is suitable for use in the present invention, and may include, but not be limited to polyethylene glycol; glycerin; sorbitol; triethyl citrate; tribuyl citrate; dibutyl sebecate; vegetable oils such as castor oil; surfactants such as polysorbates, sodium lauryl sulfates, and dioctyl-sodium sulfosuccinates; propylene glycol; mono acetate of glycerol; diacetate of glycerol; triacetate of glycerol; natural gums and mixtures thereof. In solutions containing a cellulose ether film former, an optional plasticizer may be present in an amount, based upon the total weight of the solution, from about 0 percent to about 40 percent.

[0024] In one embodiment, the film forming composition for dip coating substrates may be substantially free of gelatin, i.e., e.g. contains less than about 1%, or less than about 0.01% of gelatin.

[0025] In another embodiment, the film forming composition for dip coating substrates may be substantially free of bovine derived materials, i.e., e.g. contains less than about 1%, or less than about 0.01% of bovine derived materials.

[0026] In embodiments wherein a cellulose ether film former is used in the composition, the film forming composition for dip coating substrates may be substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

[0027] In yet another embodiment, the film forming composition for dip coating substrates may be substantially free of plasticizers, i.e., e.g. contains less than about 1%, or less than about 0.01% of plasticizers.

[0028] In one embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to less than about 100 percent, e.g. from about 95 percent to about 99.5 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.5 percent to about 5 percent of a thickener such as a hydrocolloid, e.g., xanthan gum.

[0029] In another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 40 percent to about 60 percent, e.g. from about 50 percent to about 55 percent, of a modified starch, e.g. a waxy maize starch, a tapioca dextrin, and/or mixtures and derivatives thereof; from about 15 percent to about 30 percent, e.g., from about 20 percent to about 25 percent of a plasticizer, e.g., glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about 25 percent, e.g., from about 10 percent to about 20 percent, of a thickener, e.g., sucrose, dextrose, fructose, maltodextrin, polydextrose, and mixtures thereof.

[0030] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose.

[0031] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose, and is substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

[0032] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 95 percent to about 100 percent, e.g. from about 97 percent to about 100 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.1 percent to about 1.0 percent, e.g. from about 0.25 percent to about 0.5 percent of a plasticizer such as vegetable oils, e.g. Castor Oil.

[0033] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total dry solids weight of the composition, from about 5 percent to about 99 percent, e.g. from about 50 percent to about 90 percent, or from about 80 percent to about 90 percent of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; from about 1 percent to about 80 percent, e.g. from about 5 percent to about 50 percent or from about 5 percent to about 40 percent of an extender, such as polycarbohydrates, e.g. maltodextrin; and from about 0.1 percent to about 20 percent, e.g. from about 2.5 percent to about 15 percent of a plasticizer such as glycols, e.g. polyethylene glycol. Examples of suitable dry compositions are disclosed in, for example, United States Patent Nos. 5,470,581 and 6,183,808, which are incorporated by reference herein.

[0034] These film forming compositions are typically in the form of a dispersion for ease of dip coating substrates therein. Such dispersions contain a solvent in an amount, based upon the total weight of the dispersion, from about 30 percent to about 97 percent, for example, from about 80 percent to about 92 percent or from about 40 percent to about 75 percent. Examples of suitable solvents include, but are not limited to water; alcohols such as methanol, ethanol, and isopropanol; organic solvents such as methylene chloride, acetone, and the like; and mixtures thereof. In one embodiment, the solvent is water. The resulting film forming dispersion typically possesses a solids level of, based upon the total weight of the film forming dispersion, from about 3 percent to about 70 percent, for example, from about 8 percent to about 20 percent or from about 25 percent to about 60 percent.

[0035] In one embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 20 percent, e.g. from about 8 percent to about 15 percent or from about 10 percent to about 14 percent, of a film former such as hydroxypropylmethylcellulose and from about 0.05 percent to about 0.2 percent, e.g. from about 0.08 percent to about 0.16 percent or from about 0.1 percent to about 0.14 percent, of a thickener such as xanthan gum.

[0036] In another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 20 percent to about 35 percent, e.g. from about 25 percent to about 30 percent, of a film former such as waxy maize starch, tapioca dextrin, and/or derivatives and mixtures thereof; from about 5 percent to about 20 percent, e.g., from about 10 percent to about 15 percent of a plasticizer such as glycerin, polyethylene glycol, propylene glycol, castor oil, and mixtures thereof; and from about 5 percent to about

15 percent of a thickener selected from sucrose, fructose, dextrose, maltodextrin, polydextrose, and mixtures thereof.

[0037] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 16 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose.

[0038] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 16 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose, and is substantially free of hydrocolloids, i.e., e.g. contains less than about 1%, or less than about 0.01% of hydrocolloids.

[0039] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 5 percent to about 25 percent, e.g. from about 8 percent to about 20 percent or from about 10 to about 16 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; and from about 0.001 percent to about 0.1 percent, e.g. from about 0.01 percent to about 0.09 percent of a plasticizer such as vegetable oils, e.g. castor oil.

[0040] In yet another embodiment, the film forming composition for dip coating substrates contains, based upon the total wet weight of the dipping dispersion composition, from about 1 percent to about 21 percent, e.g. from about 10 percent to about 19 percent or from about 16 percent to about 19 percent, of a film former such as a cellulose ether, e.g., hydroxypropylmethylcellulose; from about 0.1 percent to about 17 percent, e.g. from about 1 percent to about 11 percent or from about 1 percent to about 8 percent of an extender, such as polycarbohydrates, e.g. maltodextrin; and from about 0.02 percent to about 4 percent, e.g. from about 0.5 percent to about 3 percent of a plasticizer such as glycols, e.g. polyethylene glycol.

[0041] Optionally, the composition for dipping may further comprise other ingredients such as, based upon the total weight of the dipping solution, from about 0 percent to about 2 percent preservatives such as methylparaben and propylparaben, from about 0 percent to about 14 percent opacifying agents such as titanium dioxide, and/or from about 0 percent to about 14 percent colorants. See *Remington's Practice of Pharmacy*, Martin & Cook, 17th ed., pp. 1625 - 30, which is herein incorporated by reference.

[0042] Any coloring agent suitable for use in pharmaceutical applications may be used in the present invention and may include, but not be limited to azo dyes, quinopthalone dyes, triphenylmethane dyes, xanthene dyes, indigoid dyes, iron oxides, iron hydroxides, titanium dioxide, natural dyes, and mixtures thereof. More specifically, suitable colorants include, but are not limited to patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D&C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, antyhocyanines, turmeric, cochineal extract, clorophyllin, canthaxanthin, caramel, betanin, and mixtures thereof.

[0043] In one embodiment, each end of the tablet or capsule may be coated with dip coatings of different colors to provide a distinctive appearance for specialty products. See United States Patent No. 4,820,524, which is incorporated by reference herein.

[0044] In one embodiment, the pharmaceutical dosage form is comprised of a) a core containing an active ingredient; b) an optional first coating layer comprised of a subcoating that substantially covers the core; and c) a second coating layer on the surface of the first coating layer, the second coating layer comprised of the dip coating composition of the present invention. As used herein, "substantially covers" shall mean at least about 95 percent of the surface area of the core is covered by the subcoating.

[0045] In an alternate embodiment, a first active ingredient may be contained in the first coating layer, and the core may contain a second active ingredient and/or an additional amount of the first active ingredient. In yet another embodiment, the active ingredient may be contained in the first coating layer, and the core may be substantially free, i.e., less than about 1 percent, e.g. less than about 0.1 percent, of active ingredient.

[0046] The use of subcoatings is well known in the art and disclosed in, for example, United States Patent Nos. 3,185,626, which is incorporated by reference herein. Any composition suitable for film-coating a tablet may be used as a subcoating according to the present invention. Examples of suitable subcoatings are disclosed in United States Patent Nos. 4,683,256, 4,543,370, 4,643,894, 4,828,841, 4,725,441, 4,802,924, 5,630,871, and 6,274,162, which are all incorporated by reference herein. Additional suitable subcoatings include one or more of the following ingredients: cellulose ethers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose; polycarbohydrates such as xanthan gum, starch, and maltodextrin; plasticizers including for example, glycerin, polyethylene glycol, propylene glycol, dibutyl sebecate, triethyl citrate, vegetable oils such as castor oil, surfactants such as polysorbate-80, sodium lauryl sulfate and dioctyl-sodium sulfosuccinate; polycarbohydrates, pigments, and opacifiers.

[0047] In one embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 2 percent to about 8 percent, e.g. from about 4 percent to about 6 percent of a water-soluble cellulose ether and

from about 0.1 percent to about 1 percent, castor oil, as disclosed in detail in United States Patent No. 5,658, 589, which is incorporated by reference herein. In another embodiment, the subcoating may be comprised of, based upon the total weight of the subcoating, from about 20 percent to about 50 percent, e.g., from about 25 percent to about 40 percent of HPMC; from about 45 percent to about 75 percent, e.g., from about 50 percent to about 70 percent of maltodextrin; and from about 1 percent to about 10 percent, e.g., from about 5 percent to about 10 percent of PEG 400.

[0048] The dried subcoating typically is present in an amount, based upon the dry weight of the core, from about 0 percent to about 5 percent. The dried dip coating layer typically is present in an amount, based upon the dry weight of the core and the optional subcoating, from about 1.5 percent to about 10 percent.

[0049] The average thickness of the dried dip coating layer typically is from about 40 to about 400 microns. However, one skilled in the art would readily appreciate without undue experimentation that the dip coating thickness may be varied in order to provide a smoother, easier to swallow, dosage form or to achieve a desired dissolution profile. Moreover, the thickness of dipped film coatings may vary at different locations on the substrate depending upon its shape. For example, the thickness of the coating at an edge or corner of a substrate may be as much as 50 percent to 70 percent less than the thickness of the coating at the center of a major face of the substrate. This difference can be minimized by, for example, use of a thicker subcoating, or use of dipping compositions that result in higher weight gains on the substrate.

[0050] In embodiments wherein a thicker dip coating is desired, we have found that an effective amount of a weight gain enhancer selected from the group consisting of simethicone, polysorbate 80 and mixtures thereof, may be added to a film forming composition comprised, consisting of, and/or consisting essentially of a film former and an optional thickener such as a hydrocolloid. The weight gain enhancer is used in an amount sufficient to increase the weight gain of the coating solution, e.g. by at least about 10 percent, by at least about 20%, or by at least about 30 % on a substrate when dried. The percent weight gain increase is determined based upon the difference between the total weight of the coated substrate with the coating composition including the weight gain enhancer, and the total weight of an coated equivalent substrate, which has been coated under similar processing conditions with a coating composition that does not include an effective amount of weight gain enhancer.

[0051] In one embodiment, the film former is a cellulose ether such as HPMC, and the thickener is a hydrocolloid such as xanthan gum and the weight gain enhancer is simethicone.

[0052] A suitable film forming composition capable of achieving increased weight gain of dip coating on a substrate may contain, based upon the total dry weight of the film forming composition, from about 40 percent to about 99.9 percent, e.g. from about 95 percent to about 99.5 percent, or from about 40 percent to about 60 percent of a film former; from about 0 percent to about 60 percent , e.g. from about 0 percent to about 10 percent, or from about 0.5 percent to about 5 percent, or from about 10 percent to about 25 percent of a thickener; and from about 0.01 percent to about 0.25 percent, e.g. from about 0.03 percent to about 0.15 percent of a weight gain enhancer. When aesthetics of the final tablet are of particular concern, it is recommended to not use greater than about 0.25 percent of a weight gain enhancer. As shown above, the amount of thickener suitable for use in the composition will vary depending upon, for example, the particular thickener selected and the desired properties of the coating. For example, when xanthan gum is the thickener of choice, the amount of xanthan gum thickener may range, based upon the total dry weight of the film forming composition, from about 0.5 percent to about 5 percent.

[0053] The film forming compositions of the present invention may be prepared by combining the film former, the thickener, and any optional ingredients such as plasticizers, preservatives, colorants, opacifiers, the weight gain enhancer, or other ingredients with the solventusing a high shear mixer until homogeneous under ambient conditions. In embodiments wherein a waxy maize starch derivative is used as a film former, the mixture may be heated to a temperature of about 60 °C to about 90 °C for faster dispersion of the ingredients. Alternatively, the film former and thickener may be preblended as dry powders, followed by addition of the resulting powder blend to the water and optional weight gain enhancer with high speed mixing. In order to remove substantially all of the bubbles from the resulting mixture, the pressure may then be decreased to about 5 inches Hg while reducing the mixing speed in order to avoid creating a vortex therein. Any other additional optional ingredients may then be added thereto at constant mixing.

[0054] It has surprisingly been found that substrates may be dipped into such solutions of the present invention using the same equipment and similar range of process conditions as used for the production of dip molded, gelatin-coated tablets. For example, both tablets and hard capsules may be coated using the aqueous dispersions of the present invention via known gelatin-dipping process parameters and equipment. Details of such equipment and processing conditions are known in the art and are disclosed at, for example, United States Patent No. 4,820,524 , which is incorporated by reference herein. Advantageously, because the coating solutions of the present invention are fluid at room temperature and are less susceptible to microbial growth than gelatin compositions, the dip coating process may occur under ambient temperature and pressure conditions.

[0055] The tablets dip coated with the composition of the present invention may contain one or more active agents. The term "active agent" is used herein in a broad sense and may encompass any material that can be carried by or entrained in the system. For example, the active agent can be a pharmaceutical, nutraceutical, vitamin, dietary sup-

plement, nutrient, herb, foodstuff, dyestuff, nutritional, mineral, supplement, or flavoring agent or the like and combinations thereof.

[0056] The active agents useful herein can be selected from classes from those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAEDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

[0057] Active agents that may be used in the invention include, but are not limited to: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; centrizine and its hydrochloride; cetirizine; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine; clorfibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine; danthron; dexbromopheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fexofenadine; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine; flurbiprofen; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron; griseofulvin; growth hormone; guafenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loperamide, loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metoclopramide and its halides/hydrates; metronidazole; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine; phenytoin; pimenol; piroxicam and its salts; polymicin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and nap-

sylate; pramiracetin; pramoxine and its hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochlorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thiethylperazine and its maleate; timolol and its maleate; thioperidone; tramadol; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripelennamine and its hydrochloride; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B_1, B_2, 8_6, B_{12}, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Active agents may further include, but are not limited to food acids; insoluble metal and mineral hydroxides, carbonates, oxides, polycarbophils, and salts thereof; adsorbates of active drugs on a magnesium trisilicate base and on a magnesium aluminum silicate base, and mixtures thereof. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

[0058] In one embodiment, the dosage forms coated with the dip coatings of the present invention provided for immediate release of the active ingredient, i.e. the dissolution of the dosage form conformed to USP specifications for immediate release tablets containing the particular active ingredient employed. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. See USP 24, 2000 Version, 19 - 20 and 856 (1999).

[0059] We have unexpectedly found that the coatings formed by dipping substrates into the compositions of the present invention possessed excellent properties comparable to those possessed by gelatin coatings, e.g. crack resistance, hardness, thickness, color uniformity, smoothness, and gloss. Typically, the coatings of the present invention possessed a surface gloss of greater than about 150, e.g. greater than about 190 or greater than about 210 when measured according to the method set forth in example 7 herein.

[0060] In addition, tablets dip coated with the compositions of the present invention were superior to tablets dip coated with conventional gelatin-based coatings in several important ways. First, tablets dip coated with the compositions of the present invention advantageously retained acceptable dissolution characteristics for the desired shelf-life and storage period at elevated temperature and humidity conditions. In particular, thehe cellulose-ether based compositions according to the present invention were also advantageously more resistant to microbial growth, which thereby enabled a longer shelf-life or use-life of the dipping solution as well as a reduction in manufacturing cost. Second, the sugar-thickened dipping dispersions according to the present invention beneficially employed a lower water content relative to that of gelatin-containing dispersions, which thereby enabled a shorter drying cycle time. Although the water content of the other dipping dispersions of the present invention may have been higher than that typically found in gelatin-based dipping solutions, the cellulose-ether based compositions of the present invention surprisingly required a shorter drying cycle time relative to that for gelatin-containing compositions. Third, the dried coatings comprised of the compositions of the present invention also surprisingly and advantageously contained fewer air bubbles relative to the amount present in dried, gelatin based dipping compositions. Fourth, unlike dip processing with gelatin-containing compositions, substrates may optionally be dipped in the solutions of the present invention at room temperature, which is economically more beneficial. Fifth, the dip coated compositions of the present invention possessed a higher degree of glossiness relative to similar coatings applied via spray coating methods known in the art. The dip coated compositions of the present invention also possessed a similar degree of glossiness relative to that possessed by gelatin-containing dip or enrobing coatings, which are currently viewed as the industry benchmark for high gloss coatings. See, e.g., United States Patent No. 6,274,162 (Typical gloss readings for standard, commercially available gel-dipped or gelatin enrobed tablets range from about 200 to 240 gloss units, gloss readings for standard, commercialy available sugar-coated medicaments range from 177 to 209 gloss units, and gloss readings for a new, high-gloss coating system range from about 148 to about 243 gloss units.).

[0061] We have further unexpectedly found that the addition of an effective amount of weight gain enhancer to a film forming composition comprised of film former and hydrocolloid not only significantly increased the resulting dry weight of the dip coating on a substrate, but it also improved the color uniformity of the coating.

[0062] The invention illustratively disclosed herein suitably may be practiced in the absence of any component, ingredient, or step which is not specifically disclosed herein. Several examples are set forth below to further illustrate the nature of the invention and the manner of carrying it out. However, the invention should not be considered as being limited to the details thereof.

EXAMPLES

Example 1.) Preparation of Subcoating Dispersions

[0063] An aqueous dispersion containing the ingredients set forth in Table A was prepared by combining all of the ingredients in a beaker under ambient conditions.

Table A:

Aqueous Dispersion Subcoating Composition	
Ingredient	**Part***
HPMC (2910, 5 mPs) from Dow Chemical Company under the tradename, "Methocel E-5"	20
Castor oil	1
Water	241.5
Total Coating Solution	262.5
% solids in coating solution	8%

* expressed in terms of part by weight unless otherwise noted

[0064] Additional aqueous dispersions containing the ingredients in Table B were similarly prepared:

Table B:

Aqueous Dispersion Subcoating Compositions					
Ingredient	**Ex 1A****	**Ex 1B**	**Ex 1C**	**Ex 1D**	**Ex 1E**
HPMC 2910, 5 mPs	20	40	40	28	28
Castor oil	1	0	0	0	0
water	212.3	566.67	566.67	566.67	566.67
maltodextrin	0	53	53	67	67
PEG 400	0	7	7	5	5
Hydroxyethyl -cellulose*	0	0	0	0	0
Total coating solution	233.3	666.67	666.67	666.67	666.67
Wt % solids in coating solution	9%	15%	15	15	15

* Available from Aqualon, under the tradename, "Natrosol 250L"

** all values expressed in terms of parts by weight unless otherwise noted

[0065] Additional aqueous dispersions containing the ingredients in Table C were similarly prepared:

Table C:

Aqueous Dispersion Subcoating Compositions			
Ingredient	**Ex 1F****	**Ex 1G**	**Ex 1H**
water	566.67	566.67	690.4
maltodextrin	71	71	0
Castor oil	0	0	0.13
HPMC (1910, 5mPas)	0	0	32.4
PEG 400	5	5	0
Hydroxyethyl-cellulose*	24	24	0

* Available from Aqualon, under the tradename, "Natrosol 250L"

** all values expressed in terms of parts by weight unless otherwise noted

Table C: (continued)

Aqueous Dispersion Subcoating Compositions			
Ingredient	**Ex 1F****	**Ex 1G**	**Ex 1H**
Total coating solution	666.67	666.67	722.9
Wt % solids in coating solution	15%	15%	4.5%

** all values expressed in terms of parts by weight unless otherwise noted

Example 2.) Preparation of Subcoated Tablets

[0066] Compressed tablets were prepared in accordance with the procedure set forth in Example 1 of United States Patent No. 5,658,589 ("'589 Patent"), which was incorporated by reference herein.

[0067] The dispersion of Example 1 was then applied onto the compressed tablets via spraying in accordance with the procedure set forth in the examples of the '589 Patent . As shown in Table D below, the dried subcoated tablets possessed an average 2% to 4% weight gain relative to the weight of the subcoating-free tablets.

[0068] This process was repeated with additional compressed tablets, but with the substitution of each, respective subcoating dispersion produced in Example 1A to 1H for that of Example 1. The percentage weight gain of the dried subcoated tablets are set forth below in Table D:

Table D:

% Weight Gain of Dried Subcoated Tablets	
Example Number	**% Weight Gain**
1A	2
1B	2
1C	4
1D	2
1E	4
IF	2
1G	4
1H	4

Example 3) Preparation of HPMC Coated Tablets

[0069] Aqueous HPMC dipping solutions containing the ingredients set forth in Table E were prepared:

Table E:

Composition of HPMC Dipping Solutions						
Ingredient	**Ex 3A *(g)**	**Ex 3B (g)**	**Ex 3C (g)**	**Ex 3D (%)**	**Ex 3E (%)**	**Ex 3F (%)**
HPMC E5	32.5	0	32.5	10	11	14
Water	200	200	200	89.89	88.879	85.85
HPMC (2910, 15mPs)	0	20	0		0	0
Xanthan gum	0	0	0	0.11	0.121	0.15
PEG 400	0	0	8	0	0	0
% (wt.) solids in dipping solution	14	9	17	10.11	11.121	14.15

* all values expressed in terms of weight (g) unless otherwise noted

[0070] Example 3A: Preparation Of Dipping Solution of Example 3A: HPMC was dispersed into 200 ml of deionized

water at a temperature of 70 °C. After adding about 1 wt % FD&C blue dye thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

[0071] Example 3B: Preparation of Dipping Solution of Example 3B: The procedure of Example 3A was repeated, but with substitution of HPMC (2910, 15mPs) for the HPMC E5.

[0072] Example 3C: Preparation Of Dipping Solution of Example 3C: HPMC was dispersed into 200 ml of deionized water at a temperature of 70 °C. After adding the PEG 400 thereto, the solution was mixed until homogeneous. The solution was then cooled to a temperature of about 22 °C.

[0073] Example 3D: Preparation Of Dipping Solution of Example 3D: HPMC and xanthan gum were added to purified water at a temperature of 80 °C until the powder was dispersed. After discontinuing the heat, the solution was divided into two parts. 4.35 wt. % of a yellow color dispersion available from Colorcon, Inc. under the tradename, "Opatint Yellow DD-2115" was added to the first part and mixed at a low speed until dispersed. 5.8% of a green color dispersion available from Colorcon, Inc. under the tradename, "Opatint Green DD-11000" was added to the second part and mixed at a low speed until dispersed. The two dispersed solutions were then stored under ambient conditions for about 12 hours.

[0074] Example 3E: Preparation Of Dipping Solution of Example 3E: The procedure of Example 3D was repeated, but using the components of Example 3E.

[0075] Example 3F: Preparation Of Dipping Solution of Example 3F: The procedure of Example 3D was repeated, but using the components of Example 3F.

[0076] Example 3G: Preparation of Hand-Dipped Dip Coated Tablets: The subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solutions of Example 3A for a dwell time of 1 second, removed from the dipping solution, then dried under ambient conditions.

[0077] This procedure was repeated, but with substitution of the dipping solutions of Examples 3B and 3C, respectively, for the dipping solution of Example 3A.

[0078] An observation of the resulting coatings showed the following:

Tablets Coated with Coating of Ex. 3A: The coatings were smooth, hard, and shiny, and had no bubbles or cracking. However, the coatings were non-uniform and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3B: The coating were shiny, with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

Tablets Coated with Coating of Ex. 3C: The coatings were shiny with few bubbles and no cracking. The coatings were more uniform and rough relative to those of Example 3A. The coatings were also somewhat tacky and thin, with land areas not well-covered. Upon exposure to ambient conditions for a six month period, no cracks were seen in the coatings.

[0079] Example 3H: Preparation of Production Scale Dipped Tablets: Additional subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were coated with the resulting dipping solution of Examples 3D using a commercial grade gel-dipping machine in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein.

[0080] This procedure was repeated, but with substitution of the dipping solutions of Examples 3E and 3F, respectively, for the dipping solution of Example 3D.

[0081] The average percentage weight gain of the dried dipped coatings were as set forth in Table F:

Table F:

Weight Gain of Dried Dip Coating	
Example	**% Wt. Gain of Dried Coating***
Ex. 3D	0.75 - 2.26
Ex. 3E	1.9 - 3.52
Ex. 3F	3.2 - 5.8

* Relative to weight of dried subcoating and core

[0082] This example showed that the addition of xanthan gum to the HPMC dipping solution provided a viscosity enhancement to the dip coating, and thus an increased weight gain of the dip coating on the tablets.

Example 3I: Preparation of Dipping Solution of Example 3I

[0083] The procedure of Example 3D was repeated, but using the components of Example 3I, as set forth in Table M:

Table M:

Composition of HPMC Dipping Solutions		
Ingredient	**Ex 3I *(g)**	**Ex 3J (g)**
HPMC E5	14	12
Water	85.89	87.88
HPMC (2910, 15mPs)	0	0
Xanthan gum	0.11	0.12
PEG 400	0	0
% (wt.) solids in dipping solution	14.11	12.12

* all values expressed in terms of weight (g) unless otherwise noted

Example 3J: Preparation of Dipping Solution of Example 3J

[0084] The procedure of Example 3D was repeated, but using the components of Example 3J, as set forth in Table M above.

Example 4) Preparation of Pre-gelatinized Starch-Containing Dip Coating Solutions

[0085] Dipping solutions comprised of the components set forth in Table G were prepared by dispersing 75 g of the modified waxy maize starch into 200 ml of water under ambient conditions with mixing:

Table G:

Pre-gelatinized starch-containing Dipping solutions		
Component/Other	**Example 4A***	**Example 4B**
Modified waxy maize starch (Purity® Gum 59)	75	125
water	200	200
Total weight of solution	275	325
Wt % solids in dipping solution	27	39

* all values expressed in terms of weight (g) unless otherwise noted

[0086] Dipping solutions comprised of the components set forth in Table H below were prepared by dispersing all of the components into 200 ml of water under ambient conditions with mixing until the resulting solution was clear.

Table H:

Pre-gelatinized starch-containing Dipping solutions With Simethicone of Example 4C			
Component	***Tradename***	***Supplier***	***Amount used****
Modified waxy maize starch	Purity ® Gum 59	National Starch & Chemical Co.	125
Simethicone	Antifoam®		2
Colloidal silicone dioxide	Aerosil ® A200		6
Glycerin	---	---	63.5
Sucrose	---	---	38
colorant	Opatint®		6.9

* all values expressed in terms of weight (mg) unless otherwise noted

Table H: (continued)

Pre-gelatinized starch-containing Dipping solutions With Simethicone of Example 4C			
Component	***Tradename***	***Supplier***	***Amount used****
water	---	---	200
Total solids			241.4
TOTAL solution (w/ 55% solids)			441.1

* all values expressed in terms of weight (mg) unless otherwise noted

[0087] Each side of the subcoated tablets prepared in accordance with Example 2 using the subcoating produced in Example 1H were hand-dipped into the dipping solution of Example 4A for a dwell time of about 1 second, pulled up, then dried under ambient conditions.

[0088] This procedure was repeated, but with substitution of the dipping solution of Example 4B for the dipping solution of Example 4A and with about a 3 day period between the completion of production of the dipping solution and the commencement of dip coating process.

[0089] This procedure was further repeated, but with substitution of the dipping solutions of Example 4C for the dipping solution of Example 4A and with about a 12 hour period between the completion of production of the dipping solution and the commencement of dip coating process.

[0090] An observation of the resulting coatings showed the following:

Tablets Coated With Dipping Solution of Ex. 4A: The coatings were very shiny, hard, smooth, even, and not tacky or cracked. However, the coatings were too thin, and land areas were not covered. No cracking after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4B: The coatings were smooth and shiny. Initially the land areas were covered; however, the coatings cracked after exposure to ambient conditions for a period of 6 months.

Tablets Coated With Dipping Solution of Ex. 4C: The coatings possessed excellent shine and cover, and were smooth with no cracks. No cracking after exposure to ambient conditions for a period of 2 months.

Example 5) Preparation of Pre-Gelatinized Starch-Containing Dip Coating Solutions

[0091] The procedure set forth in Example 4C is repeated, but without the inclusion of simethicone. Prior to coating the substrate, the solution is exposed to a vacuum pressure of 5 inches Hg in order to remove substantially all of the visible bubbles from the solution. The resulting coating possesses excellent shine and cover, and is smooth with no cracks.

Example 6) Effect of Simethicone on Coating Weight Gain

[0092] The following dip coating solutions set forth in Table I were prepared to illustrate the effect of simethicone as a weight gain enhancer. Amounts are percent based on the total weight of coating solution.

Table I

Dip Coating Solutions					
Ingredient	6A	6B	6C	6D	6E
HPMC 2910, 5mPs	12	12	12	12	12
Xanthan Gum	1	1	1	1	1
Simethicone	0	0.035	0.07	0.14	0.25
Yellow color dispersion***	6	6	6	6	6
Water	81	80.965	80.93	80.86	80.75

*** Yellow color dispersion was "Opatint"® No. DD2125 obtained from Colorcon, Inc.

[0093] Dipping solutions A through E, above, were prepared in the following manner: Purified water was heated to about 35°C. HPMC and xanthan gum were added while mixing using a laboratory scale electric mixer (Janke and

Kunkel, IKA Labortechnik, Staufen, Germany) with propeller blade at approximately 1000 rpm until the powders appeared uniformly dispersed. Heating was discontinued, and the resulting dispersion was allowed to stand overnight at room temperature. Simethicone and yellow color dispersion were then added with mixing at approximately 500 rpm.

[0094] Subcoated cores, prepared according to the method of example 1A, were preweighed, then dipped in solutions A, B, C, D, and E, above for a dwell time of about 2 seconds, pulled up, then dried at ambient conditions (about 22 °C). The cores were dipped simultaneously in sets of 7. Three separate sets of seven cores were dipped in each solution A through E. The average weight gain was determined from the triplicate sets of dipped cores from each coating solution.

[0095] Resulting weight gains were as follows in Table J:

Table J -

Average Weight Gain					
Dipping Solution	6A	6B	6C	6D	6E
Average weight gain from dip coat (mg/tablet)	13.3	20.8	22.3	23.7	19.1

Example 7) Surface Gloss Measurement of Coated Tablets

[0096] Tablets made according to the preceding examples were tested for surface gloss using an instrument available from TriCor Systems Inc. (Elgin, IL) under the tradename, " Tri-Cor Model 805A/806H Surface Analysis System" and generally in accordance with the procedure described in "TriCor Systems WGLOSS 3.4 Model 805A/806H Surface Analysis System Reference Manual" (1996),which is incorporated by reference herein, except as modified below,

[0097] This instrument utilized a CCD camera detector, employed a flat diffuse light source, compared tablet samples to a reference standard, and determined average gloss values at a 60 degree incident angle. During its operation, the instrument generated a greyscale image, wherein the occurrence of brighter pixels indicated the presence of more gloss at that given location.

[0098] The instrument also incorporated software that utilized a grouping method to quantify gloss, i.e., pixels with similar brightness were grouped together for averaging purposes.

[0099] The "percent full scale" or "percent ideal" setting (also referred to as the "percent sample group" setting), was specified by the user to designate the portion of the brightest pixels above the threshold that will be considered as one group and a veraged within that group. "Threshold", as used herein, is defined as the maximum gloss value that will not be included in the average gloss value calculation. Thus, the background, or the non-glossy areas of a sample were excluded from the average gloss value calculations. The method disclosed in K. Fegley and C. Vesey, "The Effect of Tablet Shape on the Perception of High Gloss Film Coating Systems", which is available at www.colorcon.com as of 18 March, 2002 and incorporated by reference herein, was used in order to minimize the effects resulting from different tablet shapes, and thus report a metric that was comparable across the industry.(Selected the 50% sample group setting as the setting which best approximated analogous data from tablet surface roughness measurements.).

[0100] After initially calibrating the instrument using a calibration reference plate (190-228; 294 degree standard; no mask, rotation 0, depth 0), a standard surface gloss measurement was then created using gel-coated caplets available from McNEIL-PPC, Inc. under the tradename, "Extra Strength Tylenol Gelcaps." The average gloss value for a sample of 112 of such gel-coated caplets was then determined, while employing the 25 mm full view mask (190-280), and configuring the instrument to the following settings:

Rotation: 0
Depth: 0.25 inches
Gloss Threshold: 95
% Full Scale: 50%
Index of Refraction: 1.57

[0101] The average surface gloss value for the reference standard was determined to be 269, using the 50% ideal (50% full scale) setting.

[0102] Samples of coated tablets prepared according to the preceding examples were then tested in accordance with the same procedure. The surface gloss values at the 50% ideal setting that were obtained are summarized in Table K below.

Table K:

Gloss values of coated tablets					
Example No.	**3D**	**3I**	**3J**	**4C**	**6B**
Type of coating	dipped	dipped	dipped	poured film	dipped
No. of tablets tested	48	48	51	plate	3
Gloss Value(% ideal at 50)	234	247	229	259	221

[0103] Additional samples of other, commercially available gel coated tablets were also tested in accordance with the same procedure and compared to the same standard. The results are summarized in Table L below.

Table L:

Gloss values of commercially available coated tablets						
Product	**Motrin IB* Caplet (white)**	**Excedrin ** Aspirin free Caplets (red)**	**Excedrin ** Migraine Geltab (green side)**	**Excedrin ** Migrain e Geltab (white side)**	**Extra Strength Tylenol Geltabs * (yellow side)**	**Extra Strength Tylenol Geltabs * (red side)**
Type of coating	sprayed film	sprayed film	gelatin enrobed	gelatin enrobed	dipped	dipped
No. of tablets tested	41	40	10	10	112	112
Gloss Value (% ideal at 50)	125	119	270	264	268	268

* Available from McNEIL-PPC, Inc.

** Available from Bristol-Myers, Squibb, Inc.

[0104] This Example showed that the tablets coated with the compositions of the present invention possessed a high surface gloss value that either was comparable to or exceeded that possessed by commercially -available gelatin coated tablets. In contrast, typical sprayed films possessed a substantially lower surface gloss, e.g. 119 to 125 in this Example.

Example 8: Preparation of Coated tablets

Example 8A: Preparation of Tablets Spray Coated With Opadry® II Subcoating

[0105] 122.8 kg (18% w/w) of a prepared blend containing HPMC 2910-6cP, maltodextrin, HPMC2910-3cP, HPMC2910-50cP, and PEG-400 (commercially available from Colorcon Inc., West Point, PA as "Opadry® II") was added with mixing into 559.7 kg (82% w/w) of 35°C purified water in a conventional pressure pot, and mixed with an air-driven propeller-type Lightnin mixer at a speed of 500 rpm. After the powder was completely added, the dispersion was mixed at 500 rpm for 2 hours, then allowed to stand without mixing at ambient conditions for 12 hours.

[0106] The resulting film coating dispersion was then applied onto compressed acetaminophen tablets, which were prepared in accordance with the procedure set forth in Example 1 of US Patent No. 5,658,589 ("'589 Patent"), which is incorporated by reference herein, via spraying in accordance with the procedure set forth in the examples of the '589 patent. The resulting spray-coated tablets possessed a 4% weight gain relative to the weight of the uncoated tablet cores.

Examples 8B: Preparation of Tablets Spray Coated with HPMC / Castor Oil Subcoating

[0107] 88.4 kg (9% w/w) of hydroxypropyl methylcellulose 2910, 5mPs and 0.347 kg (0.04% w/w) of castor Oil were mixed into 593.8 kg (91% w/w) of purified water at 35°C in a tank with mixer (Lee Industries) at a speed of 1750 rpm. After the powder was completely added, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed

was then reduced to 1750 rpm while the pressure was reduced to 15 inches of water for 2 hours to deaerate the dispersion.

[0108] The resulting film coating dispersion was then applied onto the compressed acetaminophen tablets of Example 8A via spraying in accordance with the procedure set forth above in Example 8A . The resulting spray coated tablets possessed a 4% weight gain relative to the weight of the uncoated tablet cores.

Example 8C: Preparation of Tablets Dip Coated with HPMC/Castor Oil dipping solutions

[0109] A dipping solution comprised of the components set forth in Table M below was produced:

Table M:

HPMC/Castor Oil Clear Dipping Solutions			
Example	A&B	C&D	E&F
HPMC 2910 5mPs	9%	13%	13%
Castor Oil	0.04%	0.05%	0.05%
Purified Water	90.96%	86.95%	86.95%

[0110] Purified water was heated to 80° C, then added to a Lee jacketed mix tank while mixing at a speed of 1750 rpm. After HPMC 2910, 5mPs and castor oil were added thereto with mixing, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then reduced to 1750 rpm while the temperature of the dispersion was reduced to 35 °C and the pressure was reduced to 15 inches water for deaeration. After mixing the dispersion for 2 hours, the resulting dispersion remained under constant pressure conditions for an additional 3 hours without mixing.

[0111] The colorant of Example 8C-a was then added to 96 kg of the resulting clear dipping solutions with mixing at a 1750 rpm speed in the amounts set forth in Table N below :

Table N:

HPMC/Castor Oil Colored Dipping Solutions						
Example	***8C-a***	***8C-b***	***8C-c***	***8C-d***	***8C-e***	***8C-f***
Colorant	Opatint (DD-1761)	Opatint (DD-2125)	Opatint (DD-1761)	Opatint (DD-2125)	Opatint (DD-10516	Opatint (DD-18000)
Amount of colorant (kg)	2.700	2.570	2.700	2.570	4.072	2.175
Color	red	yellow	red	yellow	blue	white
Visc/Temp	490 cps @40C	518 cps @40C	612cps @30C	457cps @30C	351cps @40C	319cps @40C
Dipping Temp	40C	40C	30C	30C	40C	40C
Weight Gain in dipping (mg/tablet)	16*	16*	26**	26**	20***	20***
Gloss	229	229	249	228	238	233

* indicates total weight gain for a tablet having an 8Ca coating on one half and an 8Cb coating on the other

** indicates total weight gain for a tablet having an 8Cc coating on one half and an 8Cd coating on the other

*** indicates total weight gain for a tablet having an 8Ce coating on one half and an 8Cf coating on the other

[0112] This procedure was independently repeated for each of the colorants set forth above in Table N.

[0113] Subcoated tablets, which were prepared in accordance with the procedure set forth above in Example 8A, were dip-coated with the dip-coating solution prepared in accordance with Example 8C-a and 8C-b using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using the dipping solution temperatures reported in the table above. This procedure was independently repeated on subcoated tablets, which were prepared in accordance with the procedure

set forth above in Example 8B, for each of the colored dipping solutions 8C-c through 8C-f in Table N above.

[0114] A visual comparison of the dip-coated tablets prepared according to examples 8C-a and 8C-b with those prepared in accordance with Examples 8C-c through 8C-f revealed that the former did not possess complete coating coverage around the edges of the tablets. By contrast, the dip-coated tablets prepared according to examples 8C-c through 8C-f possessed a superior good coating coverage around the tablet edges. This indicated that a weight gain of 16 mg per gelcap (such as that produced by the 9% HPMC formula of examples 8C-a and 8C-b) was insufficient for the HPMC/Castor Oil dipping formula, while a weight gain of 20 to 26 mg per gelcap/geltab (such as that produced by the 13% HPMC formula of examples 8C-c through 8C-f) provided good coverage.

[0115] In addition, a visual comparison of the HPMC/Castor Oil dip-coated tablets of Examples 8C-c through 8C-f and the HPMC/Xanthan Gum dip-coated tablets of Examples 3I and 3J indicated that the former possessed superior gloss and surface smoothness. The superior gloss and smoothness were likely attributed to the inclusion of castor oil in the dip coating.

Example 9: Preparation of Tablets Dip Coated with HPMC/Maltodextrin/PEG dipping solutions

[0116] 143.3 kg (21% w/w) of the Opadry® II blend of Example 8A was added into 539.2 kg (79% w/w) of 35°C purified water while mixing at a speed of 3500 rpm for 15 minutes. The mixer speed was then decreased to 1750 rpm, and the tank evacuated to 30 PSIA to deaerate the solution for 5 hours. 2.70 kg of Colorant (Opatint® Red DD-1761, from Colorcon Inc.) was then added to 96 kg of the clear dipping solution while mixing at a speed of 1750 rpm. 2.570 kg of Colorant (Opatint® Yellow DD-2125, from Colorcon Inc.) was then added to a second 96 kg portion of the clear dipping solution while mixing at a speed of 1750 rpm until dispersed.

[0117] Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 8B, were dip-coated with the dip-coating solution prepared in accordance with this Example using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using a dipping solution temperature of 30°C. The viscosity of the dipping solutions was 607 cPs at 30°C for the yellow solution, and 677 cPs at 30°C for the red solution. An average weight gain of about 27 mg/gelcap was obtained.

[0118] Seventy-two (72) dipped gel caps produced in accordance with this Example were tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped gelcaps was 258 gloss units.

Example 10: Preparation of Tablets Dip Coated with HPMC/Carrageenan dipping solutions

[0119] 88.4 kg (13% w/w) of HPMC 2910-5 mPs, 0.347 kg of Castor Oil (0.05% w/w), and 0.68 kg (0.1% w/w) of kappa Carrageenan-911 were added into a tank containing 590 kg (87% w/w) of 80°C purified water while mixing at a speed of 1750 rpm. After the addition was complete, the mixer speed was increased to 3500 rpm for 15 minutes. The mixer speed was then decreased to 1750 rpm, and the tank evacuated to 15 inches of water to deaerate the solution for 2 hours. Mixing was then stopped, and the dispersion was allowed to stand at constant pressure for an additional 3 hours. 2.175 kg of Colorant (Opatint® White DD-18000, from Colorcon Inc.) was then added to 96 kg of the clear dipping solution while mixing at a speed of 1750 rpm. 4.072 kg of Colorant (Opatint® Blue DD-10516, from Colorcon Inc.) was then added to a second 96 kg portion of the clear dipping solution while mixing at a speed of 1750 rpm until dispersed.

[0120] Subcoated tablets, which were prepared in accordance with the procedure and materials set forth above in Example 8B, were dip-coated with the dip-coating solution prepared in accordance with this Example using a commercial grade gel-dipping machine and in accordance with the procedure described in United States Patent No. 4,820,524, which is incorporated by reference herein, using a dipping solution temperature of 40°C. An average weight gain of about 20 mg/gelcap was obtained.

Eighty-eight (88) dipped gel caps produced in accordance with this Example were tested for surface gloss in accordance with the procedure set forth in Example 7. The average surface gloss for these dipped geltabs was 232 gloss units.

Claims

1. A water soluble composition for dip-coating a substrate comprised of:

   a) hydroxypropylmethyl cellulose; and
   b) a thickener selected from the group consisting of xanthan gum, carrageenan and mixtures thereof,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

2. The composition of claim 1, wherein the composition is comprised of, based upon the total dry weight of the composition,

a) from 95 percent to less than 100 percent of hydroxypropylmethyl cellulose; and
b) from 0.5 percent to 5 percent of a thickener selected from the group consisting of xanthan gum, carrageenan and mixtures thereof,.

3. The composition of claim 2 further comprising, based upon the total dry weight of the composition, up to about 40% plasticizers.

4. The water soluble composition of any one of claims 1 to 3, wherein the composition is comprised of, based upon the total dry weight of the composition:

a) greater than 95 percent and less than 99.5 percent of hydroxypropylmethyl cellulose; and
b) greater than 0.5 percent and less than 5 percent of carrageenan,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

5. A pharmaceutical dosage form comprising an outer coating of the composition of any one of claims 1 to 4.

6. A pharmaceutical dosage form comprising a core, a subcoating substantially covering said core, and an outer coating substantially covering said subcoating, wherein the outer coating is comprised of the composition of any one of claims 1 to 4.

7. The dosage form of claim 6 wherein the subcoating is comprised of, based upon the total dry weight of the subcoating,

a) from 2 percent to 8 percent of a water-soluble cellulose ether selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose and mixtures thereof.
b) from 0.1 percent to 1 percent castor oil.

8. The coated dosage form of claim 6 or claim 7, further comprising an effective amount of a pharmaceutical active ingredient, wherein said dosage form meets USP dissolution requirements for immediate release forms of said pharmaceutical active ingredient.

9. A water soluble composition for dip-coating a substrate comprised of:

a) hydroxypropylmethyl cellulose; and
b) maltodextrin,

wherein the composition possesses a surface gloss of at least 150 when applied via dip coating to a substrate.

10. Use of the composition of claim 9 for the manufacture of dip coated tablets.

11. A simulated capsule-like medicament comprising:

a. a core having a first end and a second end,
b. a first coating layer having a first color provided on said first end of said core;
c. a second coating layer having a second color on said second end of said core, said first color is different from said second color;

wherein at least one of said first coating layer and second coating layer comprises the composition of any one of claims 1 to 4.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 260 219 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
21.05.2003 Bulletin 2003/21

(51) Int Cl.[7]: **A61K 9/28**

(43) Date of publication A2:
27.11.2002 Bulletin 2002/48

(21) Application number: **02253342.6**

(22) Date of filing: **14.05.2002**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **15.05.2001 US 291127 P**
28.09.2001 US 325726 P
12.04.2002 US 122999

(71) Applicant: **McNeil-PPC, Inc.**
Skillman, NJ 08558-9418 (US)

(72) Inventors:
- **Gulian, Cynthia**
  Lansdale, PA 19446 (US)
- **Gowan, Walter G. Jr.**
  Woodstock, GA 30189 (US)
- **Parekh, Kishor B.**
  Horsham, PA 19044 (US)
- **Morris, Joseph M.**
  Coatesville, PA 19320 (US)
- **Markley, Thomas J.**
  North Wales, PA 19454 (US)
- **Wieand, Dennis C**
  Coopersburg, PA 18036 (US)
- **McNally, Gerard P.**
  Berwyn, PA 19312 (US)

(74) Representative: **Mercer, Christopher Paul et al**
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

(54) Dip coating compositions containing cellulose ethers

(57) Water soluble, gelatin-free dip coatings for pharmaceutical solid dosage forms such as tablets comprising HPMC and xanthan gum, carrageenan, and mixtures thereof, or HPMC and castor oil or maltodextrin.

EP 1 260 219 A3

Printed by Jouve, 75001 PARIS (FR)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 02 25 3342

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 591 455 A (SIGNORINO CHARLES A) 7 January 1997 (1997-01-07) * column 4, line 3 - line 14 * * column 5, line 18-28 * * examples 10-12 * * claims 1,2,6 *	1-3,5,9	A61K9/28
X	EP 0 638 310 A (SQUIBB BRISTOL MYERS CO) 15 February 1995 (1995-02-15) * page 3, line 51 - line 58 * * page 4, line 8 - line 12 *	1-3,5	
X	EP 0 714 656 A (NIPPON ELANCO) 5 June 1996 (1996-06-05) * page 5, line 18 - line 40 *	1-4	
X	WO 91 15548 A (BERWIND PHARMA SERVICE) 17 October 1991 (1991-10-17) * claims 1,23 * * page 14, line 7 - line 14 * * example 1 *	9	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	US 5 470 581 A (GRILLO SUSAN M ET AL) 28 November 1995 (1995-11-28) * examples 4,5 * * claims 1,23 *	9	A61K
X	EP 0 839 527 A (MCNEIL PPC INC) 6 May 1998 (1998-05-06) * example 2 * * claims 1-8 *	9	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	19 March 2003	Hedegaard, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 3342

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

19-03-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5591455 A	07-01-1997	US 5514384 A	07-05-1996
		US 5480479 A	02-01-1996
		AT 192335 T	15-05-2000
		AU 654991 B2	01-12-1994
		AU 9150391 A	22-07-1992
		CA 2098834 A1	21-06-1992
		DE 69132166 D1	08-06-2000
		DE 69132166 T2	21-12-2000
		EP 0569408 A1	18-11-1993
		JP 3157158 B2	16-04-2001
		JP 6504076 T	12-05-1994
		WO 9211002 A1	09-07-1992
EP 0638310 A	15-02-1995	AU 6878294 A	09-02-1995
		CA 2129099 A1	03-02-1995
		CN 1118254 A	13-03-1996
		CZ 9401810 A3	15-02-1995
		EP 0638310 A1	15-02-1995
		FI 943569 A	03-02-1995
		HU 70951 A2	28-11-1995
		IL 110376 A	16-08-1998
		JP 7145052 A	06-06-1995
		NO 942854 A	03-02-1995
		NZ 264129 A	28-05-1996
		PL 304508 A1	06-02-1995
		US 5506248 A	09-04-1996
		ZA 9405672 A	06-03-1995
EP 0714656 A	05-06-1996	JP 2959423 B2	06-10-1999
		JP 8208458 A	13-08-1996
		DE 69520194 D1	05-04-2001
		DE 69520194 T2	02-08-2001
		EP 0714656 A1	05-06-1996
		ES 2156198 T3	16-06-2001
		US 5756123 A	26-05-1998
WO 9115548 A	17-10-1991	AU 658565 B2	27-04-1995
		AU 7686491 A	30-10-1991
		DE 69121098 D1	29-08-1996
		DE 69121098 T2	23-01-1997
		DK 527153 T3	25-11-1996
		EP 0527153 A1	17-02-1993
		JP 3165438 B2	14-05-2001
		JP 5508667 T	02-12-1993
		KR 202433 B1	15-06-1999
		WO 9115548 A1	17-10-1991

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 3342

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

19-03-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9115548 A		US 5470581 A	28-11-1995
		ZA 9102430 A	29-01-1992
US 5470581 A	28-11-1995	AU 658565 B2	27-04-1995
		AU 7686491 A	30-10-1991
		DE 69121098 D1	29-08-1996
		DE 69121098 T2	23-01-1997
		DK 527153 T3	25-11-1996
		EP 0527153 A1	17-02-1993
		JP 3165438 B2	14-05-2001
		JP 5508667 T	02-12-1993
		KR 202433 B1	15-06-1999
		WO 9115548 A1	17-10-1991
		ZA 9102430 A	29-01-1992
EP 0839527 A	06-05-1998	US 5807580 A	15-09-1998
		AU 736243 B2	26-07-2001
		AU 4187197 A	07-05-1998
		CN 1183273 A	03-06-1998
		EP 0839527 A2	06-05-1998
		JP 10147517 A	02-06-1998

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

1361068

PATENT SPECIFICATION (11) 1361068

(21) Application No. 41532/71 (22) Filed 6 Sept. 1971
(31) Convention Application No. 78023 (32) Filed 5 Sept. 1970
(31) Convention Application No. 57003 (32) Filed 29 July 1971 in
(33) Japan (JA)
(44) Complete Specification published 24 July 1974
(51) International Classification A61K 27/00
(52) Index at acceptance
A5B 382 38Y 400 402 40Y 411 41Y 420 42Y 440 44Y 480 48Y 500 50Y 540 54Y 565 56Y 606 60Y 764
B1V 2AX 3A 3DX 3F

(72) Inventors RYOZO WATANABE, TADAKAZU SUYAMA, KUZUMASA YOKOYAMA and YOHEI ODAK

(54) PROCESS FOR PREPARING INJECTABLE FLUOROCARBON EMULSION CAPABLE OF CARRYING OXYGEN

ERRATUM

SPECIFICATION NO 1361068

Page 1, Heading (72) Inventors, *for* KUZUMASA YOKOYAMA and YOHEI ODAK *read* KAZUMASA YOKOYAMA and YOHEI ODAKA

THE PATENT OFFICE
14 October 1974

R 77233/7

patients suffering from severe bleeding.

Heretofore, it has been the ordinary expedient for life saving in the case of human bleeding where the loss of blood is not more than 1500 ml, to supply a transfusion containing a substance having a colloidal osmotic pressure, for example, dextran, or an electrolyte solution such as Lactate Ringer's solution, in order to prevent bleeding shock. However, where the loss of blood exceeds 1500 ml, the amount of oxygen carried by red blood-cells in blood becomes short, and tissue respiration at the peripheral tissues becomes insufficient. Therefore, life saving has been impossible in these cases unless blood transfusion is conducted.

Preparations having an ability to carry oxygen in animal bodies have been studied by a number of people, but it is only in recent years that the preparations have been shown to have a life saving effect when injected into animals. In 1966, L. C. Clark Jr. succeeed in keeping mice living for a long time by immersing the mice in some kind of fluorocarbon solutions (see Science, *152*, 1755 (1966)), and studies on utilization of fluorocarbons as an oxygen carrier in living bodies were started at that time. In 1968, R. P. oxygen, and have developed a novel process for preparing, on a mass-production scale, an injectable emulsion capable of keeping dogs and monkeys living for a long time by blood exchange transfusion.

According to the present invention, there is provided a process for preparing an injectable fluorocarbon emulsion capable of carrying oxygen, which comprises emulsifying in an aqueous salt solution with surfactant a fluorocarbon selected from perfluorobutyletetrahydrofuran, perfluorotributylamine, perfluorooctane, perfluorodecalin, perfluoromethyldecalin and 2-monohydroxy-nonacosafluoro-3,6,9,12 - tetraoxa - 5,8,11 - trimethylpentadecane, the fluorocarbon having an ability to dissolve at least 30 V/V % oxygen under a 100% oxygen atmosphere at an atmospheric pressure, centrifuging the resulting aqueous emulsion to adjust the particle size of fluorocarbon particles in the emulsion to within the range of 0.05μ to 0.25μ, and sterilising the resulting emulsion under rotation.

For example, when 20 W/V % of perfluorotributylamine is made to be contained as the fluorocarbon, the emulsion obtained according to the present invention can contain 12.5 ml of oxygen per liter, but as a result

SEE ERRATA SLIP ATTACHED

PATENT SPECIFICATION (11) 1361068

1361068

(21) Application No. 41532/71 (22) Filed 6 Sept. 1971
(31) Convention Application No. 78023 (32) Filed 5 Sept. 1970
(31) Convention Application No. 57003 (32) Filed 29 July 1971 in
(33) Japan (JA)
(44) Complete Specification published 24 July 1974
(51) International Classification A61K 27/00
(52) Index at acceptance
A5B 382 38Y 400 402 40Y 411 41Y 420 42Y 440 44Y 480 48Y 500 50Y 540 54Y 565 56Y 606 60Y 764
B1V 2AX 3A 3DX 3F

(72) Inventors RYOZO WATANABE, TADAKAZU SUYAMA, KUZUMASA YOKOYAMA and YOHEI ODAK

(54) PROCESS FOR PREPARING INJECTABLE FLUOROCARBON EMULSION CAPABLE OF CARRYING OXYGEN

(71) We, GREEN CROSS CORPORATION, a corporation organized under the laws of Japan, of 1,3-chome, Gamaucho, Joto-ku, Osaka, Japan, and TANABE SEIYAKU CO. LTD., a corporation organized under the laws of Japan, of 21 Dosho-machi-3-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a process for preparing an injectable emulsion capable of carrying oxygen, which is used in life saving of patients suffering from severe bleeding.

Heretofore, it has been the ordinary expedient for life saving in the case of human bleeding where the loss of blood is not more than 1500 ml, to supply a transfusion containing a substance having a colloidal osmotic pressure, for example, dextran, or an electrolyte solution such as Lactate Ringer's solution, in order to prevent bleeding shock. However, where the loss of blood exceeds 1500 ml, the amount of oxygen carried by red blood-cells in blood becomes short, and tissue respiration at the peripheral tissues becomes insufficient. Therefore, life saving has been impossible in these cases unless blood transfusion is conducted.

Preparations having an ability to carry oxygen in animal bodies have been studied by a number of people, but it is only in recent years that the preparations have been shown to have a life saving effect when injected into animals. In 1966, L. C. Clark Jr. succeeed in keeping mice living for a long time by immersing the mice in some kind of fluorocarbon solutions (see Science, *152*, 1755 (1966)), and studies on utilization of fluorocarbons as an oxygen carrier in living bodies were started at that time. In 1968, R. P. Geyer reported that total blood of a mouse was exchanged with a fluorocarbon emulsion by blood transfusion and the mouse could be kept living for a few hours ("Organ Perfusion and Preservation" Appleton-Centry Crafts, page 85 (1968)). Then, Clark *et al* reported that total blood of a dog was exchanged with a fluorocarbon emulsion by blood exchange transfusion, and the dog could be successfully kept living for a long time (Chemical and Engineering News, Dec. 15 (1969), page 51).

The present inventors have made studies on a preparation having an ability to carry oxygen, and have developed a novel process for preparing, on a mass-production scale, an injectable emulsion capable of keeping dogs and monkeys living for a long time by blood exchange transfusion.

According to the present invention, there is provided a process for preparing an injectable fluorocarbon emulsion capable of carrying oxygen, which comprises emulsifying in an aqueous salt solution with surfactant a fluorocarbon selected from perfluorobutyletetrahydrofuran, perfluorotributylamine, perfluorooctane, perfluorodecalin, perfluoromethyldecalin and 2-monohydroxy-nonacosafluoro-3,6,9,12 - tetraoxa - 5,8,11 - trimethylpentadecane, the fluorocarbon having an ability to dissolve at least 30 V/V % oxygen under a 100% oxygen atmosphere at an atmospheric pressure, centrifuging the resulting aqueous emulsion to adjust the particle size of fluorocarbon particles in the emulsion to within the range of 0.05μ to 0.25μ, and sterilising the resulting emulsion under rotation.

For example, when 20 W/V % of perfluorotributylamine is made to be contained as the fluorocarbon, the emulsion obtained according to the present invention can contain 12.5 ml of oxygen per liter, but as a result

SEE ERRATA SLIP ATTACHED

of further studies to obtain an emulsion having a higher oxygen content, the present inventors have found that a fluoro-carbon emulsion containing, for example, 69.0 ml of oxygen per liter can be obtained by deaerating said fluorocarbon and the aqueous salt solution under a reduced pressure before the emulsification, blowing oxygen into the deaerated fluorocarbon and aqueous salt solution thereby to dissolve the oxygen therein, then carrying out said emulsification and centrifugal separation and sterilizing the emulsion under the oxygen atmosphere under rotation. It has been found that the fluorescent emulsion having such a high oxygen content is obviously effective in improving the living body just after the loss of blood.

As the non-ionic surfactant of polyoxyethylene-polyoxypropylene system capable of emulsifying and stabilizing said fluorocarbons as an aqueous emulsion, the heretofore well-known surfactants can be used, but in view of the toxicity, molecular weight and emulsion stability, polyoxyethylene-polyoxypropylene copolymers having molecular weight of 5,000 to 15,000 particularly 8,200 to 10,500, are most suitable. Any yolk lecithin or soybean lecithin can be used as surfactants, which contain polyalchol such as glycerol or sorbitol as emulsion stabilizer.

Emulsification is carried out in the following manner. At first, a predetermined amount of the surfactant is dissolved in a suitable aqueous electrolyte solution and an oxygen-carrying material is added thereto. The resulting mixture is stirred in a homoblender or by a propeller stirrer thereby to prepare a crude emulsion. When a small amount of the emulsion is to be prepared, the crude emulsion is further emulsified in a magnetostrictive ultrasonic wave generator, and when a large amount of the emulsion is to be prepared, it is further emulsified in a Manton-Gaulin type, injection emulsifier. The emulsifying conditions for the former case are that, while the crude emulsion is kept at 40°C or less, the ultrasonic wave of 19 KC is given to the crude emulsion for 15 minutes, and those for the latter case are that, while the crude emulsion is kept at 50°C or less, the crude emulsion is injected under a pressure of 140 kg/cm² at the first stage, under a pressure of 500 kg/cm² at the second and third stages, under a pressure of 560 kg/cm² at the fourth stage and under a pressure of 140 kg/cm² at the fifth stage. Fuorocarbon particles of the thus obtained emulsion are distributed in a particle size range of 0.05μ to 1.0μ, when observed by an electron microscope. When the thus obtained emulsion is injected in an animal directly as such, a good result cannot be obtained as shown in Table 3, and it is necessary to restrict the particle size distribution to a narrower range.

To obtain an emulsion of a higher oxygen content, (1) the thus prepared emulsion is deaerated under a reduced pressure, and pure oxygen is blown into the deaerated emulsion, or (2) the fluorocarbon raw material and the aqueous salt solution are deaerated under a reduced pressure before the emulsification, pure oxygen is blown into the deaerated fluorocarbon raw material and aqueous salt solution thereby to dissolve only oxygen therein, and the thus obtained fluorocarbon raw material and aqueous salt solution are emulsified under the oxygen atmosphere according to said emulsifying procedure. Said procedure (1) is applicable to the preparation of a small amount of the emulsion, and oxygen can be contained in the emulsion theoretically at a higher concentration. However, when 100 l or more of the emulsion is to be prepared, said procedure (2) is more efficient. The differences in the oxygen content due to the difference in the procedure are given in Table 1:

TABLE 1

Oxygen content of fluorocarbon emulsion

Sample	Oxygen-replacing procedure	Oxygen content (ml) per l of emulsion
20 W/V % perfluorotributylamine emulsion A	No oxygen replacement or oxygen atmosphere is used	12.5
20 W/V % perfluorobutyl tetrahydrofuran emulsion B	Same as above	17.4
A	Procedure (1). 100 ml of oxygen gas is aerated per liter of the emulsion for one minute	49.6
B	Same as above	68.1
A	Procedure (2)	69.0
B	Same as above	93.5

The present inventors have found that a centrifugal separation is useful for finely dividing the fluorocarbon particles, and it is the first requirement for the present invention to adjust the particle size distribution to a narrower range by the centrifugal operation. A De Laval or Saval type centrifuge is suitable for the centrifugal operation, and it is advantageous in a mass production scale to continuously carry out the centrifugal separation by said centrifuge. In the case of the former De Laval type centrifuge, a type BP15 K is used and the emulsion is passed through the centrifuge at a flow rate of 30 l/hr and a supernatant liquid is collected, while setting the motor and the rotor at 1500 rpm and 900 rpm, respectively. In the case of the latter Saval type centrifuge, the emulsion is passed therethrough at flow rate of 6 l/hr, while setting the centrifuge at 1000 x g. The particle sizes of the fluorocarbon after the centrifugal separation are in a range from 0.05μ to 0.25μ, and an animal test result reveals that the thus prepared emulsion can be satisfactorily used, as shown in Table 2. To obtain an emulsion having a higher oxygen content, said centrifugal operation is carried out in the oxygen atmosphere.

To use the thus prepared emulsion as an injection material safely, it is necessary to sterilize the emulsion. When the emulsion is heated, particles of the emulsion usually start to join together and are aggregated, and consequently the emulsion undergoes phase separation. The present inventors have found that, to sterilize the emulsion without joining together and aggregating the particles, it is useful to slowly rotate the emulsion in a sterilizer. It is the second requirement for the present invention to sterilize the emulsion under rotation. For example, when the emulsion is sterilized at 115°C for 15 minutes while keeping a container for the emulsion at standstill, the emulsion undergoes complete phase separation, whereas when the emulsion undergoes rotation at 12 rpm under the same conditions as above, only slight growth of the particle sizes is observed. For example, the particle sizes of 0.05μ to 0.25μ are increased only to a range from 0.05μ to 0.375μ. When the emulsion is injected in an animal after said rotary sterilization has been effected, the best result can be obtained, as shown in Table 2. To obtain an emulsion having a higher oxygen content said rotary sterilization is carried out under the oxygen atmosphere.

The particle sizes of the fluorocarbon have been determined all from the electron microscope images, and one example of the particle size distribution is shown in Table 2.

TABLE 2

Particle sizes (μ) / Sample	0.05 — 0.25	0.25 — 0.375	0.375 — 0.5	0.5 — 0.75	0.75 — 1.0
Emulsion obtained by ultrasonic treatment	73%	18%	6%	2%	1%
Emulsion obtained by injection emulsification	72%	21%	6%	1%	0%
Supernatant emulsion obtained by centrifuge	100%	0%	0%	0%	0%
Emulsion obtained by rotary sterilization	87%	13%	0%	0 %	0%

The same particle size distribution can be observed in the case of an emulsion having a higher oxygen content.

Test result on a relation between the particle size distribution of the fluorocarbon and ratio of the dead mice to the tested mice is shown in Table 3. In this test, each sample was prepared by mixing 20 W/V % of perfluorotributylamine and 4 W/V % of polyoxyethylene-polyoxypropylene copolymer having a molecular weight of 8,200 with a lactate Ringer's solution. The circulation blood of the mice was exchanged with the sample until the hematocrit value reached 3% or less, and the living state of the mice was observed after 72 hours.

Table 3.

Particle size distribution and ratio of the dead mice

Sample (particle size distribution)	Number of dead mice per number of tested mice
Emulsion obtained by ultrasonic treatment (0.05—1.0μ)	10/10
Emulsion obtained by injection emulsification (0.05—0.75μ)	8/10
Supernatant emulsion obtained by centrifuge (0.05—0.25μ)	0/10
Emulsion obtained by rotary sterilization (0.05—0.375μ)	0/10

To ascertain the effect due to the difference in the oxygen content, the same test as in Example 3 was carried out with the emulsion [A] of Table 1. The result is shown in Table 4, where 20 Wister strain rats (weight: 120—150 g) were employed in place of the mice.

TABLE 4

Oxygen content and ratio of the dead rats

Sample	Oxygen-replacing procedure	Oxygen content (ml/l of the emulsion)	Ratio of dead rat (number) to tested rat (number)
[A]	No oxygen replacement	12.5	6/20
[A]	Procedure (1)	49.6	2/20
[A]	Procedure (2)	69.0	0/20

Now, the present invention will be explained in detail, referring to examples.

Example 1.

52.6 g of sodium chloride, 3.7 g of potassiam chloride, 1.4 g of magnesium chloride, 22.2 g of sodium acetate and 50.2g of sodium gluconate were dissolved in 1,000 ml of distilled water for injection thereby to prepare an aqueous electrolyte solution, and the resulting solution was diluted to 8 l. 500 g of polyoxyethylene-polyoxypropylene copolymer having a molecular weight of 8,200 was further dissolved therein. The resulting solution was filtered, and 1.5 kg of perfluorotributylamine was added to the filtrate. The mixture was vigorously stirred with a propeller stirrer for about 30 minutes thereby to obtain a crude emulsion. Distilled water was added to the crude emulsion to make total volume 10 l. The thus obtained crude emulsion was placed in a liquid tank of Manton-Gaulin injection-type emulsifier and emulsified by injecting the emulsion under a pressure of 140 kg/cm² at the first stage, under a pressure of 500 kg/cm² at the second and third stages, under a pressure of 560 kg/cm² at the fourth stage and under a pressure of 140 kg/cm² at the fifth stage, while keeping the temperature at 40° to 50°C.

The total amount of the thus obtained emulsion was passed through De Laval type centrifuge, type BK15K (motor: 1,500 rpm; rotor: 9,000 rpm) at a flow rate of 30 l/hr for about 20 minutes, and the supernatant emulsion was collected. However, 500 ml of the initially passed emulsion was returned to the centrifuge because of poor centrifuging effect, and recentrifuged. By the centrifugal operation, about 8 l of the emulsion containing 15 W/V % of fluorocarbon was obtained. The thus obtained emulsion was fractioned in injection vials, and the vials were plugged and placed in a rotary sterlizer. The emulsion was sterilized at 115°C under rotation at 12 rpm for 15 minutes. The emulsion after the rotary sterilization contained about 90% of fluorocarbon having particle sizes of 0.05μ to 0.25μ and about 10% of that having particle

sizes of 0.25μ to 0.375μ, but contained no fluorocarbon having larger particle sizes. The oxygen content of the thus obtained emulsion was 9.3 ml/l.

Example 2.

1.5 g of perfluorotributylamine was heated and boiled at 100°C to drive the dissolved gas out, and cooled to room temperature by passing oxygen therethrough. Further, perfluorotributylamine was subjected to pressure reduction to 40 mm Hg at 5°C to drive the dissolved gas out, and the dissolved gas was replaced with oxygen gas. Emulsification was carried out in the same manner as in Example 1, except the thus obtained perfluorotributylamine was used and all the operations were conducted under the oxygen atmosphere, whereby an emulsion having the same particle size distribution as in Example 1 and an oxygen content of 52.8 ml/l was obtained.

Example 3.

40 g of polyoxyethylene-polyoxypropylene copolymer having a molecular weight of 10,500 was dissolved in 800 ml of Ringer's solution containing sodium lactate. The thus obtained solution was filtered, and 100 g of perfluorobutyltetrahydrofuran was added to the filtrate. The resulting mixture was stirred at room temperature in a homomixer for 15 minutes, whereby a crude emulsion was obtained. The Ringer's solution containing sodium lactate was further added to the crude emulsion to make the total volume 1l. 100 ml each of the crude emulsion was emulsified in a magnetostrictive ultrasonic generator at 19 KC for 15 minutes, while keeping the temperature at 40°C or less. The thus obtained emulsions were collected and placed in a Saval type continuous centrifuge (the word SAVAL is a Trade Mark). The emulsion was centrifuged at 1000 x g by passing all the amount of the emulsion therethrough for 10 minutes, whereby about 1 l of emulsion containing about 8 W/V % of fluorocarbon was obtained. The thus obtained emulsion was sterlized under rotation under the same conditions as in Example 1, whereby an emulsion having almost same particle size distribution as in Example 1 and an oxygen content of 8.7 ml/1 was obtained.

Example 4.

Emulsification was carried out in the same manner as in Example 3, except that the perfluorobutyltetrahydrofuran deaerated under a reduced pressure whose dissolved gas was replaced with oxygen in the same manner as in Example 2 was used and all the operations were conducted under the oxygen atmosphere, whereby an emulsion having almost the same particle size distribution as in Example 1 and an oxygen content of 47.8 ml/l was obtained.

Example 5.

One kg of purified yolk lecithin was emulsified in 40 l of an aqeuous electroylte solution containing 0.9 g of sodium chloride, 1.94 g of potassium chloride, 2.24 g of sodium lactate, 0.142 g of magnesium chloride and 10 g of sorbitol in 1 l of distilled water and the resulting emulsion was filtered. Then, 5 kg of perfluoro-octane was added to the filtrate, and the mixture was vigorously stirred by a propeller stirrer, thereby to prepare a crude emulsion. The aqueous electrolyte solution having said composition was further added to the crude emulsion to make the total volume 50 l, and the emulsification, centrifuging and rotary sterilization of the crude emulsion were carried out in the same manner as in Example 1, whereby about 40 l of an emulsion containing 10% of fluorocarbon having particle sizes of 0.05μ and 0.375μ and an oxygen content of 7.3 ml/l was obtained.

Example 6.

40 kg of perfluorotributylamine was placed in a vessel capable of withstanding a pressure reduction and subjected to pressure reduction to 10 mm Hg while cooling it to 0°C. The vessel was vibrated occasionally and kept to the pressure reduction for at least 20 minutes to drive the dissolved gas out of the perfluorotributylamine completely. All the following operations were carried out carefully in the oxygen atmosphere. Then, oxygen gas was introduced into the perfluorotributylamine liquid to return the pressure reduction to the atmospheric pressure and dissolve the oxygen in the liquid. The thus obtained liquid was added to 195 l of physiologically saline water containing 4 W/V % of polyoxyethylene-polyoxypropylene copolymer having a molecular weight of 10,500, which were heated to 100°C in advance to drive the dissolved gas therefrom and then saturated with oxygen gas, and the resulting mixture was vigorously stirred for about 30 minutes by a propeller stirrer thereby to obtain a crude emulsion. The thus obtained crude emulsion was placed in a liquid tank of a Manton-Gaulin injection type emulsifier and emulsified by injecting the emulsion under a pressure of 140 kg/cm^2 at the first stage, under a pressure of 500 kg/cm^2 at the second and third stages, under a pressure of 560 kg/cm^2 at the fourth stage and under a pressure of 140 kg/cm^2 at the fifth stage, while keeping the temperature at 40° to 50°C.

The total amount of the resulting emulsion was passed through a De Laval type centrifuge, type BP15K (motor: 1,500 rpm; rotor: 9,00 rpm) at a flow rate of 30 l/hr for about 20 minutes, and the supernatant emulsion was collected. However, 500 ml of the initially passed emulsion is returned to the centrifuge because of the poor centrifuging effect and recentrifuged. By the centrifuging operation,

about 200 l of an emulsion containing 20 W/V % of fluorocrabon was obtained. The resulting emulsion was fractioned into injection vials in the oxygen atmosphere, and the vials were plugged and placed in a rotary sterilizer, where sterilization was carried out at 121°C for 15 minutes under rotation at 18 rpm. The resulting emulsion after the rotary sterilization had about 90 W/V % of fluorocarbon having particle sizes of 0.05μ to 0.25μ and about 10 W/V % of that having particle sizes of 0.25μ to 0.375μ, but contained no fluorocarbon having larger particle sizes. The oxygen content of the emulsion was 69.0 ml/l.

The present inventors exchanged blood of dogs and monkeys with the emulsions prepared in the foregoing examples until the hematocrit value reached 3%, and 18 dogs and 7 monkeys, whose almost entire blood was successfully exchanged with the emulsions by operational procedure based on transfusion, could survived normally for three months, and after three months, they were sacrificed and dissected, but no abnormal state was observed throughout all the tissues. It was recognized from that result that the fluorocarbon emulsion whose particle sizes were adjusted to 0.05μ to 0.375μ had an ability to carry oxygen and carbon dioxide through the living body as a substitute for red blood-cells.

WHAT WE CLAIM IS:—

1. A process for preparing an injectable fluorocarbon emulsion capable of carrying oxygen, which comprise emulsifying in an aqueous salt solution with surfactant a fluorocarbon selected from perfluorobutyltetrahydrofuran, perfluorotributylamine, perfluorooctane, perfluorodecalin, perfluoromethyldecalin and 2 - monohydroxy - nonacosafluoro - 3,6,9,12-tetraoxa - 5,8,11 - trimethylpentadecane, the fluorocarbon having an ability to dissolve at least 30 V/V % oxygen under a 100% oxygen atmosphere at an atmospheric pressure, centrifuging the resulting aqueous emulsion to adjust the particle size of fluorocarbon particles in the emulsion to within the range of 0.05μ to 0.25μ, and sterilizing the resulting emulsion under rotation.

2. A process according to Claim 1, wherein the surfactant is a polyoxyethylene-polyoxypropylene copolymer having a molecular weight of 8,200 to 10,500 or a yolk lecithin or a soybean lecithin.

3. A process according to Claim 1 or 2, wherein particles of the emulsion after the rotary sterilization have particles sizes of 0.05μ to 0.375μ.

4. A process according to Claim 1, 2 or 3 wherein the rotary sterilization is carried out at 115°C at 12 rpm for 15 minutes or at 121°C at 18 rpm for 15 minutes.

5. A process according to any of Claims 1 to 4, wherein the aqueous emulsion is deaerated under a reduced pressure and blown with pure oxygen gas before the centrifuging and the successive operations are all carried out in an oxygen atmosphere thereby to obtain an emulsion having a higher oxygen content.

6. A process according to any of Claims 1 to 4, wherein the fluorocarbon and the aqueous salt solution are deaerated under a reduced pressure and oxygen is blown thereinto dissolve oxygen therein in advance, and all the operations are carried out in an oxygen atmosphere.

7. A process for preparing an injectable fluorocarbon emulsion substantially as described in any one of the Examples herein.

8. An injectable fluorocarbon emulsion prepared by a process according to any preceding claim.

REDDIE & GROSE,
Agents for the Applicants,
6 Bream's Buildings,
London EC4A 1HN.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1974.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : B01D 37/00, 27/00 — A1

(11) International Publication Number: WO 93/22029

(43) International Publication Date: 11 November 1993 (11.11.93)

(21) International Application Number: PCT/US93/04021

(22) International Filing Date: 28 April 1993 (28.04.93)

(30) Priority data:
07/875,774 29 April 1992 (29.04.92) US

(71) Applicant: PALL CORPORATION [US/US]; 2200 Northern Boulevard, East Hills, NY 11548 (US).

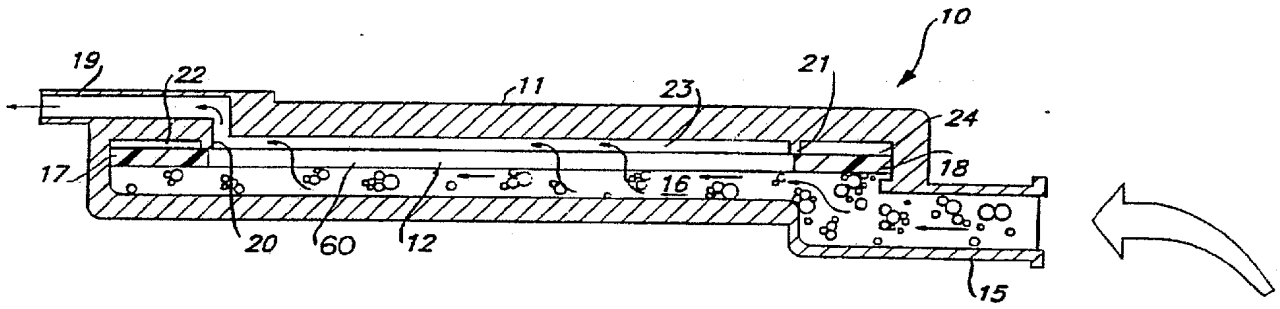
(72) Inventors: BORMANN, Thomas, J. ; 29 Cawfield Lane, Melville, NY 11747 (US). MATKOVICH, Vlado, I. ; 11 Old Estate Road, Glen Cove, NY 11542 (US). GSELL, Thomas, C. ; 40 Valentine Avenue, Glen Cove, NY 11542 (US). DELGIACCO, Gerard, R. ; 196 Tibbetts Road, Yonkers, NY 10705 (US).

(74) Agents: JAY, Jeremy, M. et al.; Suite 300, 700 Thirteenth Street, N.W., Washington, DC 20005 (US).

(81) Designated States: CA, GB, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD AND DEVICE FOR TREATING A PARENTERAL EMULSION-CONTAINING MEDICAMENT FLUID



(57) Abstract

Parenteral emulsion-containing medicament fluid is treated by passing the fluid into a filter assembly (10). The fluid is introduced via the inlet (15) into chamber (16) and the fluid then passes through a fluid filtration element (12) into chamber (23) and passes out of the filter device (10) via outlet (19). Passing the fluid through the filtration element (12) blocks microorganisms and other undesirable substances from passing therethrough. Gas which may be present in the fluid and/or the filter assembly (10) may be passed through gas venting elements (17, 18).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**MR**	Mauritania
AU	Australia	**GA**	Gabon	**MW**	Malawi
BB	Barbados	**GB**	United Kingdom	**NL**	Netherlands
BE	Belgium	**GN**	Guinea	**NO**	Norway
BF	Burkina Faso	**GR**	Greece	**NZ**	New Zealand
BG	Bulgaria	**HU**	Hungary	**PL**	Poland
BJ	Benin	**IE**	Ireland	**PT**	Portugal
BR	Brazil	**IT**	Italy	**RO**	Romania
CA	Canada	**JP**	Japan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SK**	Slovak Republic
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SN**	Senegal
CM	Cameroon	**LI**	Liechtenstein	**SU**	Soviet Union
CS	Czechoslovakia	**LK**	Sri Lanka	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**MC**	Monaco	**UA**	Ukraine
DK	Denmark	**MG**	Madagascar	**US**	United States of America
ES	Spain	**ML**	Mali	**VN**	Viet Nam
FI	Finland	**MN**	Mongolia		

Method and device for treating a parenteral emulsion-containing medicament fluid

Technical Field

This invention relates to a method, system, and device for treating parenteral fluids.

Background of the Invention

The use of parenteral fluids (e.g., involving an administrative pathway other than one which involves the gastrointestinal tract) in health care has grown rapidly over the past several years. For example, since some individuals are unable to receive medication by enteral means, and some medications are less efficient when taken enterally, the use of parenterally administered drugs is preferred.

Parenteral administration typically includes intravascular, intramuscular, or subcutaneous routes, but drugs may be applied to the skin, injected intradermally, inhaled or absorbed.

Unfortunately, while the parenteral administration of fluids such as medicaments may be advantageous, it is not without drawbacks. For example, infection during the administration process is a potential complication, even though medicaments may be produced according to strict regulations, e.g., strict aseptic protocols, and the preparation may be highly uniform. Microbiologic contamination of parenterally administered substances may occur during their preparation, during administration, or via manipulation of a part of the administration set, thus leading to infection. The threat of

infection is of particular concern when administering parenteral fluids to debilitated patients with compromised immune systems, since their resistance to infection may be low.

The problem may be magnified since parenterally administered medicaments, particularly those containing lipids, may provide a medium for the rapid growth of potentially pathogenic microorganisms. For example, fungal organisms, such as Candida albicans, and bacterial organisms such as Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus spp. may thrive in a variety of medicament administration systems, therefore posing a threat of infection. Additionally, pyrogenic substances, for example, endotoxins in the parenteral fluid, can induce fever. Moreover, failure to maintain aseptic protocols may lead to infection caused by pathogenic contaminants.

There are other drawbacks associated with parenterally administered fluids, particularly those medicaments including an oil-in-water emulsion wherein lipids are a primary component of the emulsion. The lipid emulsion is typically stabilized by an emulsifying agent which gives the emulsion droplets a negative surface charge. The negatively charged emulsion droplets repel each other, which helps maintain the homogenous dispersion of the lipid particles within the internal phase of the emulsion. If homogenous dispersion is not maintained, the emulsion may destabilize, and the particles may aggregate in larger numbers, and coalesce to form larger particles. This may pose a great threat to the patient if this parenteral fluid is administered, since particles about 5 micrometers or greater in

size may block small pulmonary vessels, causing a potentially dangerous fat embolus.

Attempts to minimize microbiological contamination and growth in parenteral administration systems have focused on the use of strict aseptic techniques and single-use products, rather than on the use of microbiological filters. For example, microbiological filters are specifically contra-indicated by some manufacturers of parenteral medicaments. It is believed that the filter may cause a breakdown of the emulsion, and the filter may exhibit limited flow capacity, may plug easily and/or may bind or restrict the flow of the medicament. Moreover, the pore rating of a microbiological filter may be expected to block desirable material, such as lipid particles in an emulsion, since those particles may have a diameter of about .5 micrometers or less.

These situations may present great risk to the patient. If the emulsion breaks down, or the medicament is blocked, the filter and administrative process may be rendered ineffective. Accordingly, medical personnel may need to constantly monitor the medicament flow, fearing that the filter may plug and have to be replaced during a medical procedure, which exposes the patient to additional risks, e.g., insufficient medication and/or septic contamination.

Furthermore, the decrease in flow of parenterally administered medicaments which pass through a microbiological filter may pose an additional drawback--excessive pressure build up. Excessive pressure build up may present a serious problem since the liquid medicament may be administered using a pump designed to operate at relatively low pressures, e.g., typically less than

15 psi. Because these pumps are not engineered to operate at higher pressures, the administration system typically includes an occlusion alarm which shuts down the pump at a relatively low pressure. This places an additional constraint on the use of anti-microbiological filters having a pore rating below about 1.2 micrometers, since these filters may exhibit pressure build up, flow restriction, and plugging that leads to pump shut down.

Thus, the administration of parenteral fluids, particularly parenteral medicaments, typically reflects an unsatisfying compromise. On the one hand, strict aseptic techniques and single use products may decrease contamination and growth without adversely affecting the emulsion or the flow rate, but these techniques still fail to provide for the administration of a bacteria-depleted infusate to the patient. On the other hand, pore ratings sufficient to remove microorganisms are typically too small to be used effectively with parenteral fluids and with some medicaments administered parenterally. This is an especially unsatisfying compromise since bacteria and/or fungi are likely to grow in media used for parenteral medicaments.

There is, therefore, a need for a filter device for a parenterally administered medicament having an enhanced capability for filtration of undesirable matter from a parenteral medicament fluid, especially to preclude microorganisms and fine particles from entering the infusate while passing the larger, desirable, parenteral medicament fluid components therethrough. In particular, there is an urgent need for a filter for processing a parenteral medicament fluid including a lipid emulsion and a medicament to remove bacteria from an infusate.

Disclosure of Invention

The present invention relates to processes and systems for treating a parenteral medicament fluid to separate undesirable material from the parenteral medicament fluid, and processing the desirable material. For example, parenteral medicament fluids, including those having lipid-based constituents, emulsions, and/or drugs, may be processed to remove biological and/or particulate contaminants from the desirable components of the parenteral medicament fluid.

The processes and systems of the present invention also provide for removal of gas from the assembly and the parenteral medicament fluid.

Brief Description of the Drawings

Figure 1 is a bottom plan view of a parenteral medicament fluid processing device according to the invention.

Figure 2 is a top plan view of the device of Figure 1.

Figure 3 is a longitudinal sectional view taken along the line III-III of the device of Figure 1.

Figure 4 is a cross-sectional view taken along the line IV-IV of the device of Figure 1.

Figure 5 is a longitudinal sectional view taken along the line III-III of the device of Figure 1.

Figure 6 is a cross-sectional view taken along the line IV-IV of the device of Figure 1.

Figure 7 is an embodiment of a parenteral medicament fluid processing system according to the invention.

Modes for Carrying Out the Invention

The present invention provides a method for

treating a parenteral emulsion-containing medicament fluid comprising passing a parenteral emulsion-containing medicament fluid to a fluid filtration element, blocking microorganisms and other undesirable material, and passing the parenteral emulsion-containing medicament fluid therethrough.

The present invention also provides a device for treating a parenteral emulsion-containing medicament fluid comprising a fluid filtration element having a microorganism blocking pore rating wherein the fluid filtration element permits the parenteral emulsion-containing medicament fluid to pass therethrough, but blocks microorganisms and other undesirable material.

The present invention also involves a system for treating and administering a parenteral emulsion-containing medicament fluid comprising a parenteral emulsion-containing medicament fluid container in fluid communication with a filter assembly including a fluid filtration element which permits the parenteral emulsion-containing medicament fluid to pass therethrough, but blocks microorganisms and other undesirable material.

The present invention may also provide processes and systems for separating gas from the parenteral emulsion-containing medicament fluid and/or from the filter assembly or system.

As used herein, a parenteral medicament fluid refers to a liquid-based solution or suspension having a medicament, preferably a drug, suitable for administration by means of a non-oral route. Medicament, as used herein, refers to a medicinal agent or any substance used in a therapeutic regimen. In a preferred embodiment, the medicament is a drug or the like. The medicament may be

soluble in water, but is preferably non-soluble in water. Non-soluble medicament fluids typically include emulsions, preferably oil-in-water emulsions, and may include amphilic molecules such as lipids. The parenteral medicament fluid may include an emulsion, a solution or a suspension including lipid substances, which are soluble in organic solvents, but are non-soluble, or slightly soluble, in water. Exemplary lipids include fatty acids, such as palmitic acid and linoleic acid; triglycerols (also known as neutral fats), such as tristearin; glycerophospholipids, such as phosphatidic acid or lecithin; sphingolipids, such as gangliosides; and steroids, such as cholesterol. It is intended that the present invention is not to be limited by the number, amount, or type of these substances. The medicament fluids of the present invention may also include any of a number of other substances, including, but not limited to, emulsifying agents, such as phospholipids and the like; stabilizers; vasoconstrictive agents; nutrients, amino acids, electrolytes, trace elements, and vitamins. It is intended that the present invention is not to be limited by the number, amount, or type of these other substances.

The parenteral medicament fluid may also include a number of undesirable materials. The undesirable elements may be present in the fluid as a result of the storage condition or environment, normal metabolic processes, or due to the processing environment, or other causes. As used herein, undesirable material refers to microorganisms, e.g., bacteria and/or fungi, as well as particulate, chemical, and other biological substances which are preferably removed or depleted from the parenteral

medicament fluid. Exemplary undesirable materials include but are not limited to particulates, and the like, typically, but not limited to coalesced particles, precipitates, pyrogenic matter such as bacterial endotoxins, administration set contaminants such as ampule and vial material, e.g., glass shards, septa bits, and the like. It is intended that the present invention is not to be limited by the type of undesirable material removed.

As illustrated in Figures 1 and 2, a parenteral emulsion-containing medicament fluid processing apparatus 10 according to the invention generally comprises a housing 11, preferably transparent, having an inlet 15 and an outlet 19, and defining a fluid flow path between the inlet and the outlet.

As depicted in Figures 1-6, in a preferred device 10, the housing 11 may include an inlet 15 and an outlet 19 defining a fluid flow path between the inlet 15 and the outlet 19 with the fluid filtration element 12 disposed across the fluid flow path. The inlet 15 may communicate with a first chamber 16 which is in fluid communication with the fluid filtration element 12 as well as with at least one, more preferably, at least two gas venting elements 17 and 18 for removing gas and the like from the parenteral emulsion-containing medicament fluid and the housing 11. In addition to the chamber 16 depicted in Figures 3-6, the housing 11 may have interior walls 20 and 21 which, in combination with the exterior walls for the housing 11, the gas venting elements 17 and 18, and the fluid filtration element 12, may define three additional chambers 22, 23, and 24. Chambers 22 and 24 may include gas vents or outlets 25 for venting to the atmosphere gas separated from and/or displaced by,

the incoming fluid.

As illustrated in Figures 3-6, the fluid filtration element 12 typically comprises a porous medium which permits an emulsion and a medicament to pass therethrough, but blocks microorganisms and other undesirable material.

In an exemplary embodiment of the invention illustrated in Figures 3 and 4, the fluid filtration element 12 may comprise a porous medium having a single layer 60.

In an exemplary embodiment of the invention illustrated in Figures 5 and 6, the fluid filtration element 12 may comprise a porous medium having multiple layers, 13, 14, 30, 40, and 50.

The parenteral emulsion-containing medicament fluid processing apparatus 10 may also include at least one, and more preferably, at least two gas venting elements 17 and 18 positioned within the housing 11, to permit gas and the like to pass therethrough, but not parenteral emulsion-containing medicament fluid. Gas in the housing passes through venting elements 17 or 18 through at least one gas vent or outlet 25 for removing gas from the housing 11. In the embodiment of the invention illustrated in Figure 1, the apparatus includes four vents 25.

A parenteral emulsion-containing medicament fluid administration system according to the invention, as shown in Figure 7, generally comprises at least one container in fluid communication with a parenteral emulsion-containing medicament fluid processing assembly which includes a fluid filtration element according to the invention.

Figure 7 shows an exemplary administration system including a parenteral emulsion-containing medicament fluid processing apparatus.

Administration set 280 may include at least one container such as syringe 200, and fluid processing apparatus 10B. In a preferred embodiment, container 200 is in fluid communication with parenteral emulsion-containing medicament fluid processing assembly 10B through conduit 210. The illustrated embodiment shows clamp 220 for controlling and/or directing the flow of parenteral emulsion-containing medicament fluid through the system, but other means for controlling and/or directing the flow may be used.

The administration system may also include at least one flow control device, e.g., pump 240, and additional clamps.

Each of the components of the invention will now be described in more detail below.

The fluid filtration element 12, in accordance with the present invention, comprises at least one porous medium suitable for passing a parenteral emulsion-containing medicament fluid therethrough, without passing microorganisms and other undesirable material. For example, the fluid filtration element may allow desirable components, such as lipids, which are typically about .5 micrometers or less in average diameter, and medicaments, to pass through, while blocking material such as coalesced particles and some microorganisms. The fluid filtration medium may also remove smaller material such as other microorganisms (e.g., bacteria), pyrogenic matter, and/or fine particles.

The porous medium, which is preferably microporous, may have a substantially uniform pore size or may include a pore size that varies in a continuous, discontinuous, or stepwise manner. Having varied pore size may contribute to lowering

the differential pressure, and may permit passing an increased volume of parenteral emulsion-containing medicament fluid. In a preferred embodiment, the porous medium has a pore size sufficient to block microorganisms and other undesirable substances, e.g., less than about 1.2 micrometers, preferably, less than about .8 micrometers, more preferably, less than about .5 micrometers, even more preferably, in the range of from about .2 to about .45 micrometers.

The fluid filtration element may have a single pore rating. In a preferred embodiment, the fluid filtration element includes a pore rating sufficient to block microorganisms and other undesirable substances, e.g., less than about 1.2 micrometers, preferably, less than about .8 micrometers, more preferably, less than about .5 micrometers, even more preferably, in the range of from about .2 to about .45 micrometers.

Pore rating, as that term is used herein, refers to the removal rating of a filtration element or porous medium in terms of measuring its efficiency in removing uniform and/or known substances, e.g., uniform diameter polystyrene microspheres in a liquid medium. For example, the pore rating may be determined using a Latex Sphere Test. Typically, a dilute suspension of spheres (0.01 to 0.1 weight percent) is prepared in water containing 0.1 weight percent Triton X-100, an octyl phenoxypolyethoxyethanol with about nine and one-half ethylene oxide units per molecule, available from Rohm & Haas Company. The size of the spheres typically varies from about 0.038 to about 5 microns. They are commercially available from Dow Chemical Company. A volume of about 10 cubic

centimeters of the suspension per square inch (of the filtration medium) is passed through the medium and the filtrate is collected in a test tube. The concentration of microspheres in the filtrate can be measured by any number of means, for example, visually, or by use of a nephelometry device (i.e., turbidity meter). The smallest diameter microsphere which is retained at a 99.9% efficiency, i.e., 999 out of 1,000, determines the pore rating.

The fluid filtration element may comprise a porous medium including a single layer. For example, in one embodiment, as illustrated in Figures 3 and 4, layer 60 may include a microorganism blocking pore rating, typically about 1.2 to about 0.1 micrometers.

A fluid filtration element according to the invention may also include a porous medium having multiple layers, i.e., two or more layers, and/or may include multiple porous media. The different layers and/or media may include different pore sizes or ratings.

Although a single pore size or pore rating and/or layer may be sufficient for filtering a variety of parenteral emulsion-containing medicament fluids including a lipid emulsion, in those embodiments wherein extensive and/or finer filtration may be desirable, the fluid filtration element may include different pore sizes and/or layers, or the porous media within the fluid filtration element may have different pore sizes, ratings and/or layers, to enhance the filtration. While the mechanism is not well understood, it is believed the filtration may reflect non-permanent deformation of the emulsion as it passes through the fluid filtration element, allowing it to pass

through pores that are smaller then the emulsion's normal diameter. Once the emulsion passes through the small pore, it may regain its normal shape and diameter without loss of its desirable characteristics. Different pore sizes and/or pore ratings may enhance filtration, e.g., by progressively deforming the components of the emulsion as they pass through the element, and/or by preventing all of the components of the emulsion from passing through a given pore at the same time, which could restrict flow.

For example, the fluid filtration element may comprise at least two layers, wherein the upstream layer has a coarser rating than the downstream layer, wherein at least the downstream pore rating blocks microorganisms and other undesirable material. The fluid filtration element may also have an intermediate layer with a coarser pore rating than the upstream layer pore rating.

Preferably, in those embodiments comprising at least two layers, the layers have different pore sizes and/or ratings, although the overall pore rating ranges for individual layers may overlap. For example, in one embodiment, as illustrated in Figures 5 and 6, the fluid filtration element 12 may comprise a first most upstream layer 13 which may include a pore rating from about 5 to about 1 micrometers, which may be a coarser pore rating than the fifth, most downstream layer 50, which may include a finer, microorganism blocking pore rating of about 1.2 to about 0.1 micrometers. Intermediate layer 40 may include a pore rating of about 50 to about 1 micrometers, and have a coarser pore rating than the most upstream first layer 13. Other inner layers, here shown as second layer 14 and third

layer 30, may have finer pore ratings than first layer 13. For example, second layer 14 may include a pore rating from about 3 to about .45 micrometers, and third layer 30 may include a pore rating from about 1.2 to about .2 micrometers. The selection of pore sizes, ratings and/or layers may be based on achieving a desired result, e.g., a low pressure drop.

The fluid filtration element may be produced from any suitable material compatible with a parenteral emulsion-containing medicament fluid, including commercially available materials. The liquid filtration element of this invention may be preferably formed, for example, from any natural or synthetic material capable of forming fibers or a membrane. Suitable polymers include, but are not limited to, polyolefins, polyesters, polyamides, polysulfones, acrylics, polyacrylonitriles, polyaramides, polyarylene oxides and sulfides, and polymers and copolymers made from halogenated olefins and unsaturated nitriles. Examples include, but are not limited to, polyvinylidene difluoride (PVDF), polyethylene, polypropylene, polybutylene terephthalate (PBT), polyethylene terephthalate (PET), and any nylon, e.g., Nylon 6, 11, 46, 66, and 610. Preferred polymers are polyolefins, polyesters, and polyamides. Especially preferred are nylon and PBT.

Other suitable materials include cellulosic derivatives, such as cellulose acetate, cellulose propionate, cellulose acetate-propionate, cellulose acetate-butyrate, and cellulose butyrate. Non-resinous materials, such as glass fibers, may also be used.

Exemplary membranes are disclosed in U.S.

Patent Nos. 4,906,374. Other membranes, including those disclosed in U.S. Patent Nos. 4,886,836; 4,964,989; 5,019,260; 4,340,479; 4,855,163; 4,774,132; 4,702,840; 4,707,266; 4,203,848 and 4,618,533, may also be suitable.

Particularly preferred are commercially available media, such as those available from Pall Corporation under the trademarks LOPRODYNE® (membranes) and HDC® (fibrous media). Commercially available membranes, such as those available from Pall Corporation under the trademarks ULTIPOR N_{66}®, ULTIPOR®, FLUORODYNE®, POSIDYNE®, CARBOXYDYNE®, IMMUNODYNE®, BIODYNE A®, BIODYNE B®, and BIODYNE C®, may also be suitable.

The membrane may comprise a microporous membrane, more preferably a skinless microporous membrane. A microporous membrane, as the term is used herein, refers to a thin sheet, generally formed from a synthetic plastic material, having a substantially uniform, continuous matrix structure containing myriad pores typically ranging from a few micrometers to about 0.04 micrometers in diameter.

The fibrous medium may comprise a fibrous matrix, more preferably, a microfibrous matrix. A microfibrous matrix, as the term is used herein, indicates a sheet-like web, or a three-dimensional network of fibers, whether melt-blown, staple, or continuous, which together form a coherent structure suitable for use as a filter medium. Preferred microfibrous matrices are made from melt-blown thermoplastic polymeric fibers, where the fiber diameter is typically in the range of from about 0.5 to about 20 micrometers, more preferably in the range of from about 1 to about 4 micrometers.

In one embodiment of the invention, the fibrous

medium comprises a synthetic, polymeric microfibrous matrix. A microfibrous matrix, partially as a result of its dirt capacity, may be more resistant to pressure build up and clogging. Additionally, a microfibrous matrix may be preferred because of its enhanced dirt capacity when compared to a microporous membrane. Moreover, a microfibrous matrix may enhance the deformation of the desirable component, e.g., a lipid particle, as the component passes through the microfibrous matrix. This deformation may be desirable in enhancing the material's ability to pass through a fine pore. Finally, the microfibrous matrix may enhance filtration by acting as a spacer. For example, in those embodiments including a membrane layer downstream of the microfibrous matrix layer, the spacer effect may prevent all of the particles from contacting the upstream surface of the membrane at the same time, which could restrict flow through the membrane.

The fluid filtration element may remain untreated, or the fibers or membrane may be treated to increase its effectiveness. There are a number of methods for treating the fluid filtration element to increase its effectiveness. For example, the fibers and/or the membrane may be surface modified to provide a low affinity for amide or peptide group-containing materials, particularly proteinaceous materials. The fibers and/or the membrane may be surface modified to affect the critical wetting surface tension (CWST) of the element. The fibers and/or membrane may be modified with a charge modifying agent to produce a negatively or positively charged medium, and/or a negative or positive zeta potential. Preferably,

the fibers and/or the membrane are charge neutral.

Surface characteristics of a fiber and/or membrane can be modified by chemical reaction including wet or dry oxidation, by coating or depositing a polymer on the surface, or by a grafting reaction. Grafting reactions may be activated by exposure to an energy source such as gas plasma, heat, a Van der Graff generator, ultraviolet light, or to various other forms of radiation, or by surface etching or deposition using a gas plasma treatment. The preferred method for a grafting reaction uses gamma-radiation, for example, from a cobalt source. The preferred method for gas plasma treatment uses a low temperature gas plasma. More preferably, the gas plasma is an inorganic gas, for example, oxygen.

An exemplary technique for gas plasma treatment may employ at least one of an inorganic and organic gas, which may be a vaporized organic material such as an ethylenic monomer to be plasma polymerized or deposited on the surface of the substrate (e.g., the fibers and/or membrane). A typical technique, e.g., radio frequency (RF) discharge, involves placing a substrate to be gas plasma treated in a vacuum chamber and bleeding gas at low pressure into the system until the desired gas pressure differential is obtained. An electromagnetic field may be generated by subjecting the gas to a capacitive or inductive RF electrical discharge. The gas absorbs energy from the electromagnetic field and ionizes, producing high energy particles. The resultant plasma modifies the fibers or medium in the plasma zone.

Inorganic gases suitable for use in gas plasma treatment may be exemplified by helium, argon,

nitrogen, neon, nitrous oxide, nitrogen dioxide, oxygen, air, ammonia, carbon monoxide, carbon dioxide, hydrogen, chlorine, hydrogen chloride, bromine cyanide, sulfur dioxide, hydrogen sulfide, xenon, krypton, and the like. Suitable organic gases may be exemplified by acetylene, pyridine, gases of organosilane compounds and organopolysiloxane compounds, fluorocarbon compounds and the like.

As noted earlier, the fibers and/or membrane may be treated to modify the CWST of the fluid filtration element. For example, the fibers and/or membrane may be subjected to radiation or a plasma stream in the presence of an acrylic monomer such as hydroxethyl methacrylate (HEMA) or hydroxypropyl acrylate (HPA) to increase the CWST of the element. Preferably, the fluid filtration element according to the invention includes a CWST in the range of about 30 dynes/cm to about 115 dynes/cm. In one embodiment, the fluid filtration element is hydrophilic, i.e., having a CWST greater than 72 dynes/cm. In a more preferred embodiment, the CWST may be in the range from about 75 to about 90 dynes/cm.

As used herein, and as disclosed in U.S. Patent 4,954,256 and in greater detail in U.S. Patent 4,925,572, the CWST of a porous medium, in units of dynes/cm, is defined as the mean value of the surface tension of the liquid which is absorbed and that of the liquid of neighboring surface tension which is not absorbed within a predetermined amount of time. The absorbed and non-absorbed values depend principally on the surface characteristics of the material from which the porous medium is made and secondarily on the pore size characteristics of

the porous medium.

In a preferred embodiment, the fluid filtration element may be surface modified by grafting thereon a hydroxyl-containing monomer to provide an element having a low affinity for amide or peptide-group containing materials, e.g., proteinaceous materials. As used herein, low affinity for proteinaceous materials refers to adsorption of less than about 100 micrograms per square centimeter of proteinaceous materials as measured by the Bovine Serum Albumin Adsorption test. In a more preferred embodiment, the adsorption of proteinaceous material is less than about 35 micrograms per square centimeter.

For example, as described in U.S. Patent 4,906,374, the fluid filtration element of this embodiment of the invention may be a polymeric substrate which may be surface modified using hydroxyl-containing unsaturated monomers, more typically monofunctional unsaturated monomers rich in pendant hydroxyl groups or groups capable of reacting to form hydroxyl groups, which are capable of undergoing polymerization and covalently bonding to the substrate under the influence of ionizing radiation.

Preferred monomers have moieties characterized by ethylenic or vinylic unsaturation and hydroxyl groups. Preferred monomers include hydroxyalkyl acrylates in which the "alcoholic" or hydroxyl-containing portion of the molecule (as opposed to the portion of the molecule "derived" from a carboxylic acid) constitutes a substituted lower alkyl group having from 2 to 5 carbon atoms, preferably from 2 to 3 carbon atoms. The substituent is preferably a hydroxyl group.

Mixtures of monomers may also be used. The most preferred hydroxyl-containing monomers are those in which the hydroxyl group is pendant, i.e., the group is not attached to a carbon atom which forms part of the polymer's backbone but is bound to a carbon atom that is separated from the backbone as, for example, a branching carbon atom. Exemplary preferred monomers include 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, 3-hydroxypropyl acrylate, and 3-hydroxypropyl methacrylate, which may be commercially available from, for example, Rohm and Haas Chemical Company under the trademark ROCRYL®.

In addition to the structural features designated above, suitable monomers may also be further characterized by their properties, such as responding to ionizing radiation by forming a free radical. Suitable monomeric compounds should be substantially completely, if not totally, soluble in the solvents used. Preferred solvents include polar solvents, particularly hydroxylated solvents such as water, lower aliphatic alcohols, such as ethanol, and mixtures thereof.

Solutions of the monomer compound may range in concentration of the monomer(s) from about 0.1 to about 5.0 percent, by weight, preferably about 0.2 to about 3.0 percent, by weight, based on the total weight of the solution. The procedure used to saturate the porous polymeric support is known to one of skill in the art. For example, batch or continuous processes may be suitable. After saturation, the monomer(s) may be polymerized and covalently bound to the polymeric substrate under the influence of ionizing radiation, more preferably, gamma radiation or short wavelength ultraviolet radiation.

The fluid filtration element may be fashioned in a variety of ways. For example, it may include one or more of the following: a web, a sheet, and a depth filter. The fluid filtration element may be formed into any geometric shape or form suitable for passing a parenteral emulsion-containing medicament fluid therethrough. Preferably, the fluid filtration element comprises at least one flat planar sheet, although in a less desirable embodiment, it may comprise at least one sheet formed into a pleated, corrugated, or accordion form.

The fluid filtration element, which may be fibrous and/or membranous, may comprise a composite or a multilayer arrangement. Layers may be individually prepared and bonded together by various means known to those skilled in the art. Layers may be contiguous and/or separate. The fluid filtration element may be preformed to form an integral unitary structure. The fluid filtration element may also include additional constituents, including, but not limited to at least one layer to provide support and/or better drainage. Exemplary supports and/or drainage components are non-woven polyester or polypropylene mesh.

The layers or porous media which constitute the fluid filtration element may be arranged in a variety of ways with respect to fluid flow. For example, a fibrous medium may be interposed between at least one upstream membrane and at least one downstream membrane. In one embodiment, the fluid filtration element may comprise three upstream membrane layers, followed by the fibrous layer and the downstream membrane. The membrane layers may have decreasing pore ratings in the upstream to

downstream direction. The fibrous layer may have a coarser pore rating than at least one of the upstream membrane layers.

The fluid filtration element of devices made in accordance with this invention may be preformed to controlled dimension and pore size and/or rating in order to form an integral, self-contained element prior to assembly in a housing. Preforming eliminates the pressure on the inlet and outlet faces of the container which may be inherent, e.g., in a packed fiber system. Pre-forming the element typically leads to devices having longer service life, coupled with better removal of undesirable material and less hold up of fluid, when compared to devices that use fibers or fibrous webs packed in a housing at assembly.

A fluid filtration element produced in accordance with the present invention for passing parenteral emulsion-containing medicament fluid preferably may have a flow area of about .65 cm^2 to about 929 cm^2 (about .1 to about 144 in^2), more preferably in the range from .65 cm^2 to about 97 cm^2 (about .1 to about 15 in^2). As used herein, the term flow area refers to the face surface area contacted by the parenteral emulsion-containing medicament fluid.

A preferred relative voids volume may be in the range of about 50% to about 90%, more preferably in the range of from about 60% to about 85%. The thickness of the fluid filtration element may be in the range of from about .008 cm to about .25 cm (about 0.003 inches to about 0.100 inches), more preferably in the range of from about .013 cm to about .25 cm (about 0.005 to about 0.100 inches). The fiber surface area of the fluid filtration

element may be in the range of from about .2 to about 2.5M^2/g, preferably from about .5 to about 2M^2/g.

In other embodiments that may involve lower flow rates and/or volumes of parenteral emulsion-containing medicament fluids, e.g., involving parenteral emulsion-containing medicament fluids for neonatals, the element area may be adjusted as necessary.

Included within the scope of the present invention are the use of other pore ratings, pore sizes and/or arrangements of fibers and membranes, with respect to particular layers as well as throughout the fluid filtration element. These alternatives may be chosen based on achieving a desired result, e.g., relating to the flow rate, the pressure drop, the type of fiber and/or membrane used, as well as other considerations.

A filter device of the subject invention may include at least one, and more preferably, two, gas venting elements 17 and 18, each comprising at least one porous medium which is liquid-repellant or non-wettable by the parenteral emulsion-containing medicament fluid and which allows gas that may be present in the parenteral emulsion-containing medicament fluid and the assembly to pass out of the device, for example, through vent 25. In a preferred embodiment, the gas venting element comprises at least one microporous membrane.

The gas venting element may vent gas from the system, in order to prime the device and eliminate any extraneous gas. This may be desirable since the presence of gas may reduce the efficiency of the fluid filtration element, e.g., by blocking the filtration element. Preferably, the gas venting

element may prevent gas from being administered, e.g., to a patient.

As used herein, gas refers to any gaseous fluid, such as air, sterilized air, oxygen, carbon dioxide, and the like; it is intended that the invention is not to be limited thereby.

The gas venting element may be oriented in a variety of ways with respect to the flow of the parenteral emulsion-containing medicament fluid. For example, the gas venting element may be located in any of the various components of the filter assembly or the administration system. By way of illustration, at least one gas venting element may be included in at least one of the conduits used to connect the various components of the administration system, in a wall of a container, or in a port on or in one of the containers or the filter assembly. Generally, however, it is preferred to include the gas venting element within the filter assembly located in the same plane as the fluid filtration element.

The gas venting element should have the necessary strength to handle the pressures encountered in use and have the ability to provide the desired permeability without the application of excessive pressure.

The gas venting element may be produced from any suitable material which is compatible with the parenteral emulsion-containing medicament fluid, including commercially available materials. The gas venting element may be formed, for example, from the materials listed above with respect to the liquid separation element. Preferred polymers are polyolefins, polyesters, polyamides, polyurethanes, polysulfones, and fluoropolymers such as

polyvinylidene difluoride, polytetrafluoroethylene, and perfluoroalkoxy resins. Particularly preferred are fluoropolymers, more preferably, polytetrafluoroethylene (PTFE).

Exemplary gas venting elements include, but are not limited to, those disclosed in U. S. Patent Nos. 4,954,256, and 5,126,054; and International Publication Nos. WO 91/17809 and WO 92/07656.

The gas venting element may be untreated, or treated or modified to make it more effective. The element may be liquophobic. A liquophobic gas venting element in the context of this invention is one that has a critical wetting surface tension lower than the surface tension of the parenteral emulsion-containing medicament fluid, or is not readily or spontaneously wetted by the parenteral emulsion-containing medicament fluid. Because the liquophobic element is not wettable, or poorly wettable, by the parenteral emulsion-containing medicament fluid being treated or processed in the system, gas in the system that contacts the liquophobic medium may pass through it, while the parenteral emulsion-containing medicament fluid may not.

The gas venting element may be treated to increase its liquophobicity. For example, the element may be surface modified to decrease the critical wetting surface tension (CWST), with the term CWST being as defined above with respect to the fluid filtration element.

In one embodiment, the gas venting element may have a CWST of less than about 28 dynes/centimeter, rendering it liquid-repelling or non-wetting by liquids with surface tensions well below that of water's surface tension of 72 dynes/centimeter.

Surface characteristics of the gas venting element may be modified by a number of methods, including those described above with respect to the fluid filtration element.

In a preferred embodiment of the gas venting element according to the subject invention, the element may comprise an untreated PTFE microporous membrane commercially available from, for example, W. L. Gore Associates, Inc.

In another embodiment of the gas venting element of the subject invention, the element may be surface modified by bonding thereon one or more fluorine-containing monomers. For example, as described in U.S. Patent 4,954,256, a porous structure, preferably a microporous, polymeric membrane comprising a fluoropolymer substrate, more preferably a poly(vinylidene fluoride) membrane substrate, may be saturated with a solution comprising one or more polymerizable fluorine-containing monomers containing an ethylenically unsaturated group and a fluoroalkyl group in a suitable solvent, and exposed to gamma radiation to form a superstrate fluoropolymer chemically bonded to the membrane.

The selected pore rating of the gas venting element may effectively preclude wetting at the operating pressures utilized for processing the parenteral emulsion-containing medicament fluid. For example, a gas venting element having a pore rating of about 0.02 micrometers operated in a typical administration system may vent gas without passing parenteral emulsion-containing medicament fluid therethrough.

With respect to pore ratings, since the gas venting element may be open to the atmosphere to

allow the gas to be vented, which could allow bacteria to enter, the pore rating should be about 0.3 micrometers or less, more preferably in the range of about 0.2 to about .02 micrometers, to preclude bacteria from entering either the system or the parenteral emulsion-containing medicament fluid.

The gas venting element may include a plurality (i.e., two or more) of layers. The element may include additional constituents, including, but not limited to, at least one liquophilic layer and/or at least one layer to provide support. As used herein, liquophilic refers to a medium that has a critical wetting surface tension higher than the surface tension of the parenteral emulsion-containing medicament fluid, or is readily or spontaneously wetted by the parenteral emulsion-containing medicament fluid. As with the fluid filtration element, the layers of the gas venting element may be individually prepared and bonded together by various means known to those skilled in the art.

The fluid filtration element 12, with or without the gas venting element 17 and 18, may be positioned across the parenteral emulsion-containing medicament fluid flow path within a housing 11 having an inlet 15 and an outlet 19 to form a filter assembly. The parenteral medicament fluid filter assembly may comprise any housing containing a fluid filtration element suitable for passing emulsion and medicament therethrough, but blocking microorganisms and other undesirable material.

The housing may be fabricated from any suitably rigid, impervious material, including any impervious thermoplastic material, which is compatible with the fluid being processed. For example, the housing may be fabricated from a metal, such as stainless steel,

or from a polymer. In a preferred embodiment, the housing is fabricated by injection molding from a polymer, more preferably a transparent or translucent polymer, such as an acrylic, polypropylene, polystyrene, or a polycarbonated resin. The housing may be diethylhexylphthalate (DEHP) free and/or phthalate free.

The housing may include an arrangement of one or more channels, grooves, conduits, passages, ribs or the like which may be serpentine, parallel or curved, or a variety of other configurations to provide for more efficient flow of parenteral emulsion-containing medicament fluid and/or gas.

The surfaces of the housing contacting the fluid may be treated or untreated. For example, the surfaces of the housing contacting the fluid may be rendered liquophilic for better priming. Methods for treating the surface of the housing include but are not limited to radiation grafting and gas plasma treatment.

Any housing of suitable shape to provide an inlet, an outlet, and an adequate flow area may be employed. The filter assembly in accordance with this invention may be fashioned in a variety of configurations including, but not limited to, those described in U. S. Patent 3,803,810.

Preferably, the filter assembly may have a hold up volume of about 50 milliliters or less. Preferred configurations, as depicted in Figures 1-6, can be constructed with a hold up volume of less than about 40 milliliters, more preferably, less than about 25 milliliters; or with a hold up volume of less than about 5 milliliters, more preferably, less than about 2 milliliters.

All of the components of the filter assembly

may be variously configured with respect to parenteral emulsion-containing medicament fluid flow. For example, the inlet 15 may be configured as a spike which can be inserted into a container of parenteral emulsion-containing medicament fluid. Alternatively, as shown in the drawings, both the inlet and the outlet can be configured as tube connectors. The chambers may be configured in a variety of ways, e.g., to maximize fluid contact with the fluid filtration element, minimize hold up volume, and/or decrease the pressure drop.

In a less desirable embodiment, gas venting element may be located in a separate housing or conduit, with or without at least one of the following: a chamber; a gas vent or outlet; a cap; and a clamp.

The fluid filtration element may be sealed or fit within the housing to achieve convenience of use, rapid priming, and efficient air clearance. Suitable techniques for sealing or fitting the medium within the housing are known to those skilled in the art.

The fluid filtration assembly in accordance with the invention may be fashioned to operate at the range of pressures encountered in use. For example, the fluid filtration assembly typically operates at pressures of less than about 25 psi, more preferably less than about 15 psi, and even more preferably, less than about 10 psi.

Since different parenteral emulsion-containing medicament fluids may be administered in different quantities, for different amounts of time and/or at different rates, the volumetric capacity of the assembly may vary. For example, a typical volumetric capacity for a parenteral emulsion-

containing medicament fluid such as an anesthetic may be less than about 1 liter, more preferably, in the range of from about 2 or about 3 milliliters to about 500 milliliters.

The filter assembly may be incorporated into a parenteral emulsion-containing medicament fluid processing and/or administration set.

The containers 200 which may be used in the parenteral emulsion-containing medicament fluid administration set may be constructed of any material compatible with a parenteral emulsion-containing medicament fluid. The composition of the container may vary on the nature of the parenteral emulsion-containing medicament fluid or fluids utilized. For example, the container may be DEHP free and/or phthalate free. A wide variety of suitable containers are already known in the art. Typically, container 200 may be composed of a flexible material, for example, polyvinyl chloride (PVC). Alternatively, the containers may be composed of a non-flexible material, for example, polypropylene, acrylonitrile butadiene styrene (ABS), polycarbonate, or stainless steel. Exemplary containers include a syringe or a flexible bag. It is intended that the invention should not be limited by the type or composition of the container being employed.

As with the containers, the conduits 210 may be constructed of any material that is compatible with the parenteral medicament fluid, preferably PVC. The conduits may be DEHP free and/or phthalate free. As used herein, the conduits are any tubing or means which provide fluid communication between the various components of the administration set. A clamp, seal, stopcock, valve, transfer leg closure,

or the like, may be in fluid communication with at least one of the conduits in order to facilitate a desired function, i.e., establishing a desired flow path for parenteral medicament fluid and/or gas.

It is intended that the present invention is not to be limited by the above listed components of the administration set. For example, the parenteral medicament fluid administration set may have components such as, but not limited to, additional containers, means to provide fluid communication and/or establish a desired flow path, and injection ports.

The invention also includes methods for treating and administering a parenteral emulsion-containing medicament fluid comprising passing an emulsion-containing medicament fluid to a fluid filtration element, blocking microorganisms and other undesirable material, and passing desirable components of the parenteral medicament fluid therethrough. A method according to the invention may also include passing gas present in the filter assembly and/or in the parenteral medicament fluid through a gas venting element, and blocking the parenteral medicament fluid from passing therethrough. A method may also include further processing the treated parenteral medicament fluid by administering it to a patient.

Parenteral medicament fluid may be passed through the fluid filtration element and administered for any length of time. Accordingly, fluid may be administered over a short period of time, e.g., to provide a bolus dose for several minutes, or fluid may be administered over a long period, e.g., to provide a sedative dose over several days. The administration of a sedative dose

over several days may be particularly advantageous when the patient has suffered serious injury, e.g., head trauma.

Using Figures 1-6 for reference, a method according to the invention may include passing a parenteral emulsion-containing medicament fluid into filter assembly 10 via the inlet 15, and, as depicted by the arrows in Figure 3, into chamber 16. The parenteral medicament fluid then passes through the fluid filtration element 12 into chamber 23, and passes out of the filter device 10 via the outlet 19. Passing the medicament fluid through the fluid filtration element may include blocking microorganisms and other undesirable substances from passing therethrough. Passing gas present in the parenteral medicament fluid and/or the filter assembly may include passing gas into the chamber 16 and, as depicted by the arrows in Figure 4, passing the gas freely through the gas venting elements 17 and 18 into the chambers 22 and 24 and out the gas outlets or vents 25.

An exemplary method may also include treating a parenteral emulsion-containing medicament fluid by passing it through an administration system wherein the parenteral medicament fluid in a container is passed from the container through a conduit and a filter assembly which includes a fluid filtration element. Passing the parenteral emulsion-containing medicament fluid through the fluid filtration element may include blocking microorganisms and other undesirable material.

For example, as shown in Figure 7, clamp 220 is opened, and a pressure differential is created, e.g., by depressing the plunger on syringe 200, such that parenteral emulsion-containing medicament fluid

passes from the container 200, through conduit 210, and through the filter assembly 10B. As fluid passes through the system, gas ahead of the fluid may be passed out of the filter assembly 10B through vents 17 and 18 and outlets 25. As the parenteral medicament fluid passes through the filter assembly 10B, desirable components of the parenteral emulsion-containing medicament fluid pass through the fluid filtration element within the assembly, while microorganisms and other undesirable material are blocked. The filtered medicament fluid then passes out of the filter assembly 10B, through conduit 210, and into another container or into the patient.

With respect to administration of the treated parenteral emulsion-containing medicament fluid, a flow control device, e.g., a pump 240, more preferably an infusion pump, even more preferably an infusion pump with at least one occlusion alarm (not shown) located either upstream or downstream of the filter assembly may be used to control the flow rate during administration. It is intended that the present invention is not to be limited by the use or type of flow control device.

Flow rates of the fluid may range from about several milliliters per hour to about 2000 milliliters per hour, as desired. A typical flow rate for a parenteral emulsion-containing medicament fluid may be from about 60 milliliters per hour to about 2000 milliliters per hour.

In a more preferred embodiment, passing the parenteral emulsion-containing medicament fluid through the fluid filtration element 12 removes microorganisms and other undesirable material from the parenteral emulsion-containing medicament fluid

with a pressure drop of about 20 psi or less, preferably about 15 psi or less, and even more preferably, 10 psi or less while passing the parenteral emulsion-containing medicament fluid at a flow rate of up to about 1200 milliliters per hour.

If desired, additional fluids, including parenteral medicament fluids, may be introduced into the system through other components of the administration set, e.g., injection ports and/or connectors located upstream and/or downstream of the filter assembly.

In a less desirable embodiment, gas may be separated from the parenteral emulsion-containing medicament fluid through a gas venting element that does not act in concert with the fluid filtration element. For example, gas venting element may be located downstream, or, more preferably, upstream, of the filter assembly, e.g., in a separate housing located in conduit 210. For example, the venting element may be located upstream of the filter assembly, and a clamp 220 located between the filter assembly and the venting element may be closed, so that creating a pressure differential causes gas displaced by the parenteral emulsion-containing medicament fluid to pass through the venting element. Once the gas has been displaced, the clamp may be opened. The gas venting element may include an additional liquophilic layer (preferably upstream of the liquophobic layer) that, once wetted, precludes the entrance of air. In another embodiment, the configuration of the housing including the gas venting element may provide for capping and uncapping the gas venting element as desired.

Examples

The filter assemblies used in the following Examples were primed before testing as follows: A 60 cc syringe was filled with a parenteral emulsion-containing medicament fluid. The filter assembly was held above the level of the syringe, and, while holding the assembly with the outlet facing up, the plunger of the syringe was manually depressed, causing the parenteral emulsion-containing medicament fluid to flow through the assembly, while gas flowed through the venting element and exited from the assembly. The housing was tapped gently to dislodge air bubbles. Once primed, the filter assembly was tested as noted below.

The parenteral emulsion-containing medicament fluid used in the following Examples was DIPRIVAN® (Stuart Pharmaceuticals), which is a hypnotic agent for use in the induction and maintenance of anesthesia. DIPRIVAN® includes propofol in an oil-in-water emulsion which also includes soybean oil, glycerol, lecithin and sodium hydroxide. Propofol is chemically described as 2,6-diisopropylphenol, with a molecular weight of 178.27.

Example 1.

A filter assembly having a housing, a fluid filtration element in the form of a flat microporous ULTIPOR N_{66}® membrane having a microorganism blocking pore rating as noted below, and a CWST of 76 $\pm$ 4 dynes/cm, along with two gas venting elements, which were flat PTFE membranes (W. L. Gore Associates, Inc.), each having a nominal pore rating of about 0.02 micrometers and a CWST of 23 dynes/centimeter, was used in the three tests in this Example.

In the first two tests, the fluid filtration

element was a microporous ULTIPOR N_{66}® membrane, supported as disclosed in U. S. Patent No. 4,340,479, with a microorganism blocking pore rating of about 0.45 micrometers.

The fluid filtration element in the third test, which had a microorganism blocking pore rating of 0.2 micrometers, was formed by co-drying two microporous ULTIPOR N_{66}® membranes, the upstream membrane having a pore rating of about 0.2 micrometers, and the downstream membrane having a pore rating of about 0.8 micrometers.

The fluid filtration element and gas venting elements were sealed in a housing to form a filter assembly as generally described with respect to Figures 1-6.

Tubing was connected from the outlet to a 50 ml graduated cylinder. Tubing was connected from the inlet to a 60 cc plastic syringe, with a 0-15 psi pressure gauge interposed in the tubing between the syringe and the inlet. The syringe had been previously filled with 60 ml of DIPRIVAN®, and the filter assembly had been primed as noted above. The syringe was mounted in a Harvard Apparatus Inc. programmable syringe pump (Model 44).

The Harvard pump was programmed to run at a bolus (or induction) rate of 20.0 ml/min for 20 ml of DIPRIVAN®, and operated according to the manufacturer's instructions. Three tests were performed, and the pressure was recorded during each test, with the following results:

Test 1 (pore rating of about 0.45 micrometers). Final pressure was about 9.2 psi.
Test 2 (pore rating of about 0.45 micrometers). Final pressure was about 9.3 psi.

Test 3 (pore rating of about 0.2 micrometers). Final pressure was about 12.0 psi.

Example 1 showed that fluid filtration elements having membranes with microorganism blocking pore ratings of about 0.45 and about 0.2 micrometers will pass a parenteral emulsion-containing medicament fluid therethrough at a bolus rate of 20.0 ml/min.

Example 2.

A filter assembly having a fluid filtration element with a microorganism blocking pore rating of about 0.45 micrometers was set up and tested as generally described with respect to Figure 1, with the exception that the Harvard pump was programmed to run at a maintenance rate of 1.0 ml/min for 20 ml of Diprivan®.

Pressure was recorded several times during the test, with the following results:

volume (ml)	pressure (psi)
3.5	.5
5.0	1.3
6	1.7
7	2.1
9	2.8
10	3.2
12	3.8
14	4.3
15	4.6
17	5.2
18	5.4
20	5.9

Example 2 showed that a fluid filtration element having a membrane with a microorganism

blocking pore rating of about 0.45 micrometers will pass a parenteral emulsion-containing medicament fluid therethrough at a maintenance rate of 1.0 ml/min.

Example 3.

The filter assembly used in this example was set up and tested as in the previous examples, with the following exceptions: 1) the fluid filtration element was a LOPRODYNE® membrane having a microorganism blocking pore rating of about 0.45 micrometers and a CWST of 83 dynes/cm, and an adsorption of proteinaceous material as measured by the Bovine Serum Albumin Adsorption test of less than about 15 micrograms per square centimeter, and 2) the same filter assembly was tested at an induction rate of 20.0 ml/min for 20 ml of DIPRIVAN®, and then at a maintenance rate of 1.0 ml/min for 40 ml of DIPRIVAN®.

The results are listed below. The first value (i.e., at 20.0 ml) reflects the pressure at the induction rate, while the remaining values reflect the pressures at the maintenance rate.

volume (ml)	pressure (psi)	
20.0	5.8	induction rate
20.5	1.3	maintenance rate
21.0	2.0	
23.0	2.7	
25.0	3.0	
30	3.7	
35	4.3	
40	4.8	
45	5.4	
50	5.8	
55	6.3	

60	6.8

Example 3 demonstrated that a fluid filtration element having a membrane which has a microorganism blocking pore rating of about 0.45 micrometers and a low affinity for amide-group containing materials will pass a parenteral emulsion-containing medicament fluid including a lipid emulsion therethrough, with less of a pressure drop than other membranes having similar microorganism blocking pore ratings. Furthermore, Example 3 demonstrated this at different rates, i.e., at a bolus rate of 20.0 ml/min, and at a maintenance rate of 1.0 ml/min.

Example 4.

The filter assembly used in this example was set up and tested as in Example 3, using an ULTIPOR N_{66}® membrane having a microorganism blocking pore rating of about 0.45 micrometers in a housing as generally described in Example 1.

The results were as follows:

volume (ml)	pressure (psi)	
20.0	9.3	induction rate
20.5	3.0	maintenance rate
21.0	4.2	
22.0	5.7	
23.0	6.1	
25	6.6	
30	7.6	
35	8.5	
40	9.3	
45	9.9	
50	10.3	
55	10.7	

60 10.9

Examples 3 and 4 demonstrated that a fluid filtration element having a membrane with a microorganism blocking pore rating of about 0.45 micrometers will pass a parenteral emulsion-containing medicament fluid therethrough, but at a higher pressure drop than a similarly tested membrane which has a similar microorganism blocking pore rating but also has a low affinity for amide-group containing materials.

Example 5.

This Example compared the distribution of lipid particles in filtered DIPRIVAN® to unfiltered DIPRIVAN®. The filter assembly included a LOPRODYNE® membrane having a microorganism blocking pore rating of about 0.45 micrometers as described in Example 3.

A 20 milliliter ampule of DIPRIVAN® was opened, and 5 ml of the emulsion was withdrawn and passed through the filter assembly described above and then through a dynamic light scattering (DLS) device (NICOMP Model 370) for submicron particle size analysis. Another 5 ml of the emulsion was passed through the DLS device without passing it through a filter assembly.

Gaussian analyses revealed the mean diameter of the filtered particles was 202.2 nm (about .2 micrometers), while the mean diameter of the unfiltered particles was 223.5 nm (about .22 micrometers).

Since comparison of the results showed the mean diameters for the two sets of particles were essentially the same, Example 5 demonstrated that a

fluid filtration element having a membrane with a microorganism blocking pore rating of about 0.45 micrometers will pass the lipid emulsion therethrough without adversely affecting the distribution of the lipid particles.

Example 6.

The fluid filtration element used in this example was formed of five layers of flat discs, each having a nominal diameter of 47 mm and a surface area of about 17.35 cm^2 (2.69 in^2), which were placed in a jig, as described below. Going from the upstream to the downstream direction, the first three layers were LOPRODYNE® nylon membranes with nominal microorganism blocking pore ratings of 1.2 micrometers, 0.65 micrometers, and 0.45 micrometers, respectively, and each had a CWST of 83 dynes/cm. The next layer was an HDC® microfibrous PBT layer with a pore rating of about 30 micrometers, with the smooth side of the layer facing downstream. The next layer was formed by co-drying two nylon ULTIPOR N_{66}® membranes, one having a microorganism blocking pore rating of about 0.2 micrometers and the other having a microorganism blocking pore rating of about 0.8 micrometers, as described in Example 1.

The 5 layers were clamped between the inlet and outlet halves of a housing jig, and the jig was connected to a 0-15 psi gauge, a 60 cc syringe, and a Harvard pump, and tested as generally described in Example 1, although the flow rate was 1.0 ml/min. Pressure was recorded several times during the test, with the following results:

volume (ml)	pressure (psi)
5	2.1

6	5.6
7	7.0
10	7.2
14	8.0
15	8.3
17	8.9
20	9.7

Example 7.

The fluid filtration element was set up and tested as in Example 6, except that the Harvard pump was programmed to run at a bolus rate of 20.0 ml/min for 20 ml of DIPRIVAN®. The pressure reached 14.9 psi.

Examples 6 and 7 demonstrated that parenteral emulsion-containing medicament fluids may be passed through fluid filtration elements including a number of layers having different pore ratings, and having a coarser pore rating upstream and a finer, bacterial removing (i.e., 0.2 micrometer) pore rating downstream, at a variety of flow rates, including a surge bolus rate, without excessive pressure build up, to produce a bacteria-depleted infusate. Additionally, Examples 6 and 7 demonstrated that parenteral medicament fluids may be passed through fluid filtration elements including layers having different microorganism blocking pore ratings.

Example 8.

Two filter assemblies as described in Example 3 were challenged with Moraxella, in DIPRIVAN®, at flow rates of 20 ml/min and 1.5 ml/min, respectively, using a Sage Instruments Model 351 pump. The input challenge to each assembly was a

total of 4.8×10^5 organisms in each 20 ml of DIPRIVAN®. No organisms were recovered downstream.

Example 8 demonstrated that fluid filtration elements having microorganism blocking pore ratings of about 0.45 micrometers blocked the passage of Moraxella without clogging.

Example 9.

Two filter assemblies as described in Example 3 were tested as generally described in Example 8, at a flow rate 20.0 ml/min, and challenged with Candida albicans. The input challenge to each assembly was 0.48×10^4 cfu/ml x 20 ml, which resulted in 9.6×10^5 total organisms per filter. No organisms were recovered downstream.

Example 9 demonstrated that fluid filtration elements having microorganism blocking pore ratings of about 0.45 micrometers blocked the passage of Candida albicans without clogging.

Example 10.

Two filter assemblies as described in Example 3 were tested as generally described in Example 8, at a flow rate of 20.0 ml/min, and challenged with Acinetobacter lwoffi in 20 ml of DIPRIVAN® containing either 4.8×10^5 or 5.3×10^5 total organisms. No organisms were recovered downstream.

Example 10 demonstrated that fluid filtration elements having microorganism blocking pore ratings of about 0.45 micrometers blocked the passage of Acinetobacter lwoffi without clogging.

Example 11.

Two filter assemblies similar to those described in Example 1, each having a fluid

filtration element formed from ULTIPOR N_{66}® membranes and having a microorganism blocking pore rating of about 0.2 micrometers, were tested as generally described in Example 8, at a flow rate of 20.0 ml/min, and challenged with Acinetobacter lwoffi in 20 ml of DIPRIVAN® containing 8.8×10^4 total organisms.

The filter assemblies allowed 3.5 ml of fluid to pass prior to pump failure unrelated to the function of the filter assembly. No organisms were recovered downstream.

Example 11 demonstrated that fluid filtration elements having microorganism blocking pore ratings of about 0.2 micrometers at least provide initial blockage of Acinetobacter lwoffi.

While the invention has been described in some detail by way of illustration and example, it should be understood that the invention is susceptible to various modifications and alternative forms, and is not restricted to the specific embodiments set forth. It should be understood that these specific embodiments are not intended to limit the invention but, on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

Claims:

1. A method for treating a parenteral emulsion-containing medicament fluid comprising:

passing a parenteral emulsion-containing medicament fluid to a fluid filtration element;

blocking microorganisms and other undesirable substances; and

passing the parenteral emulsion-containing medicament fluid therethrough.

2. The method of claim 1 wherein passing a parenteral emulsion-containing medicament fluid through the fluid filtration element comprises passing a parenteral medicament fluid containing an anesthetic through the fluid filtration element.

3. The method of claim 1 wherein passing the parenteral medicament fluid through a fluid filtration element comprises passing the parenteral medicament fluid through a membrane having a pore rating of less than about 0.8 micrometers.

4. The method of claim 3 wherein passing the parenteral medicament fluid through a fluid filtration element comprises passing the parenteral medicament fluid through a membrane having a pore rating of less than about 0.5 micrometers.

5. The method of claim 1 further comprising separating gas from the parenteral emulsion-containing medicament fluid.

6. The method of claim 1 wherein passing a parenteral emulsion-containing medicament fluid through a fluid filtration element comprises passing

the parenteral emulsion-containing medicament fluid through a fluid filtration element having a low affinity for amide-group containing materials.

7. A method for producing a bacterial-depleted parenteral emulsion-containing medicament fluid comprising:

passing a parenteral emulsion-containing medicament fluid to a fluid filtration element;

removing bacteria and other undesirable substances; and

passing the bacteria-depleted parenteral emulsion-containing medicament fluid therethrough.

8. A device for treating a parenteral emulsion-containing medicament fluid comprising:

a housing including an inlet and an outlet and defining a fluid flow path between the inlet and the outlet; and

a fluid filtration element having a microorganism blocking pore rating which permits parenteral emulsion-containing medicament fluid to pass therethrough, but blocks microorganisms in the parenteral emulsion-containing medicament fluid, wherein the fluid filtration element is disposed within the housing across the fluid flow path.

9. The device of claim 8 wherein the element comprises at least one membrane having a pore rating of less than about 0.8 micrometers.

10. The device of claim 9 wherein the element includes a membrane having a pore rating in the range of from about 0.45 micrometers to about 0.2 micrometers.

11. The device of claim 8 further comprising at least one gas venting element.

12. The device of claim 8 wherein the membrane has a low affinity for amide-group containing materials.

13. A system for treating a parenteral emulsion-containing medicament fluid comprising:

at least one parenteral emulsion-containing medicament fluid container; and

a fluid filtration assembly in fluid communication with the parenteral emulsion-containing medicament fluid container, said fluid filtration assembly having a fluid filtration element in a housing;

wherein said fluid filtration element has a microorganism blocking pore rating which permits parenteral emulsion-containing medicament fluid to pass therethrough, but blocks microorganisms.

14. The system of claim 13 wherein the element has a pore rating of less than about 0.8 micrometers.

15. The system of claim 13 further comprising at least one gas venting element.

FIG. 1

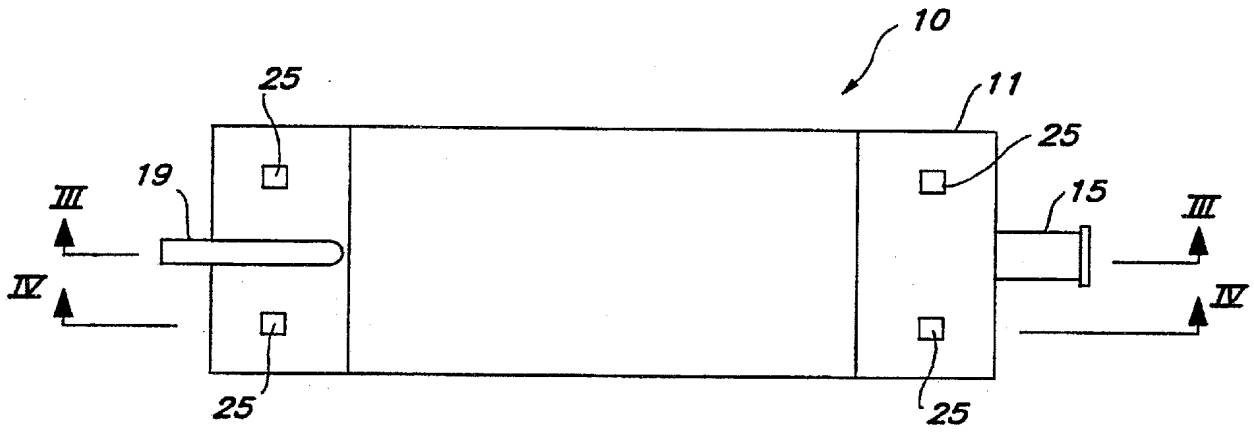


FIG. 2

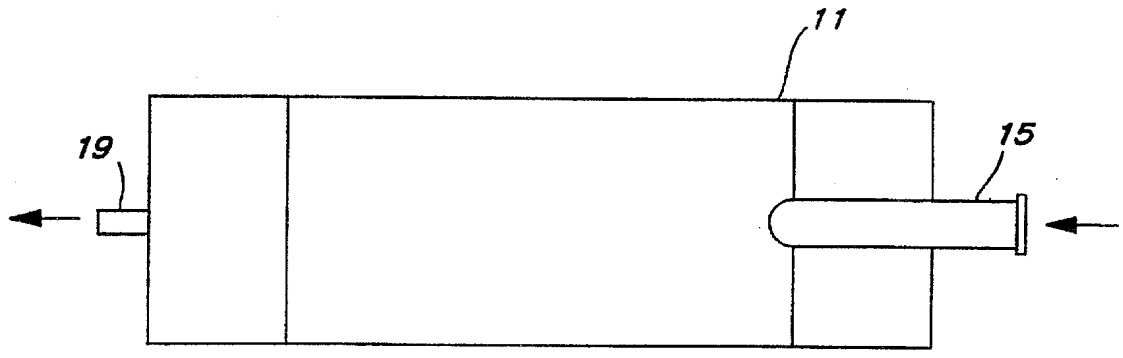


FIG. 3

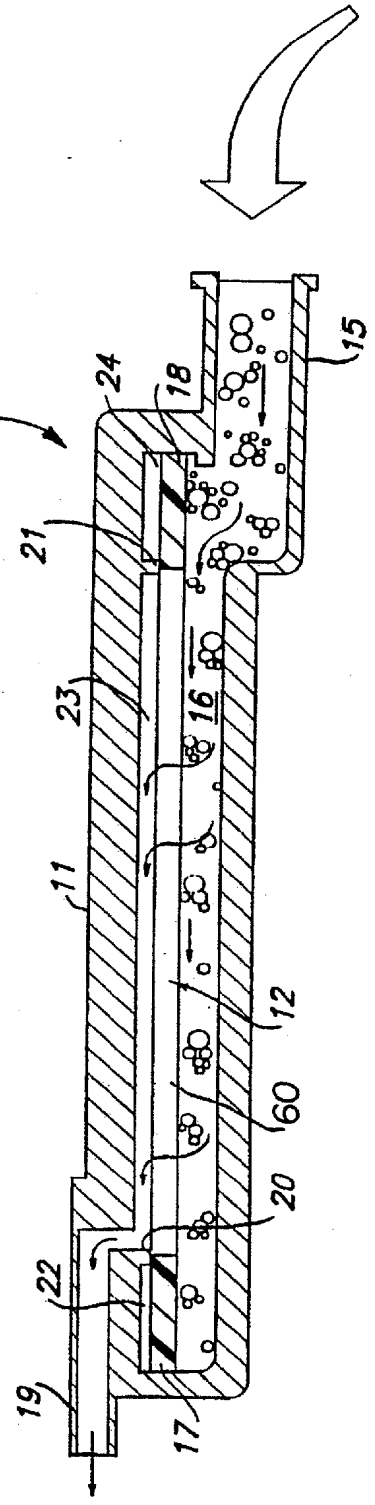


FIG. 4

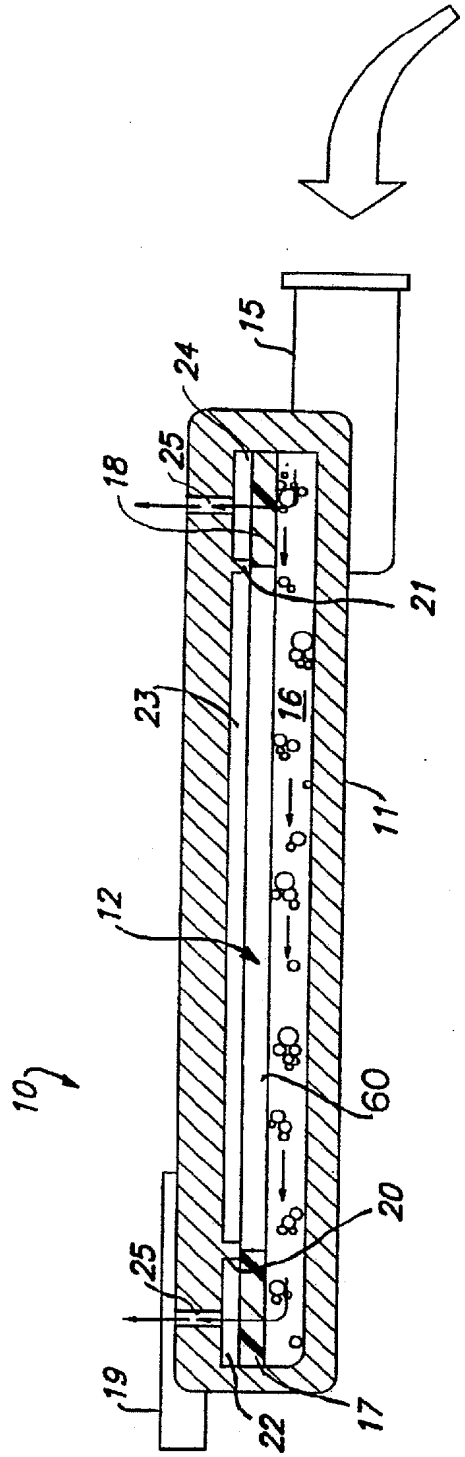


FIG. 5

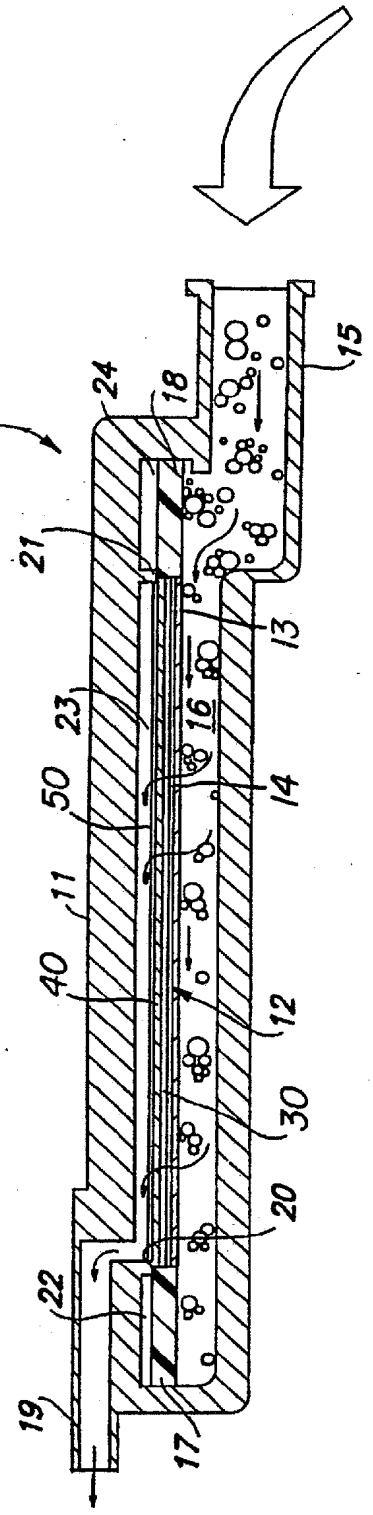
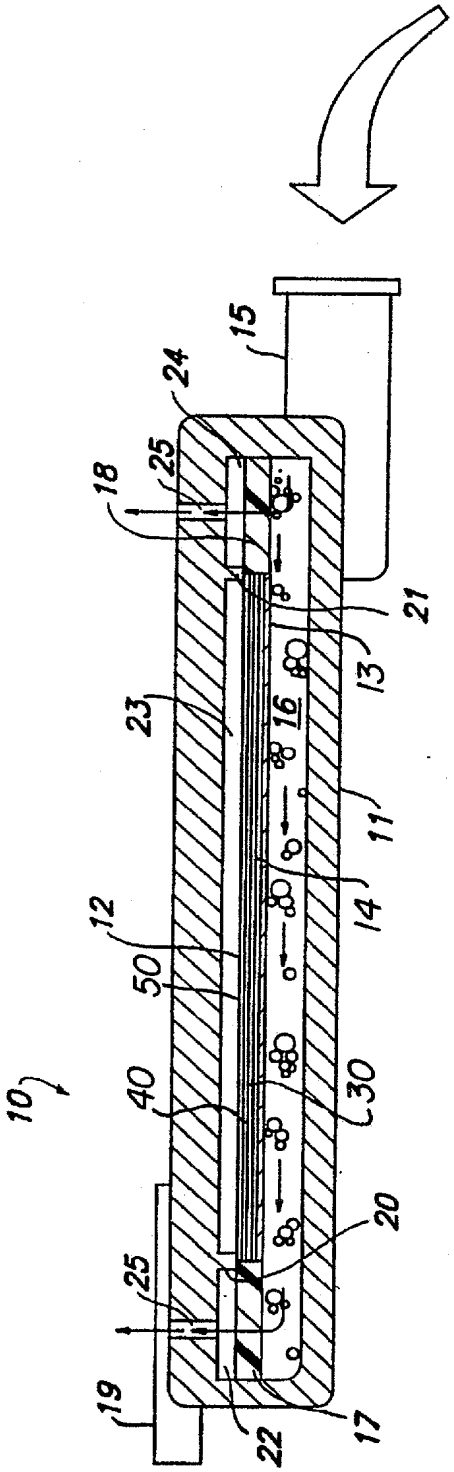


FIG. 6



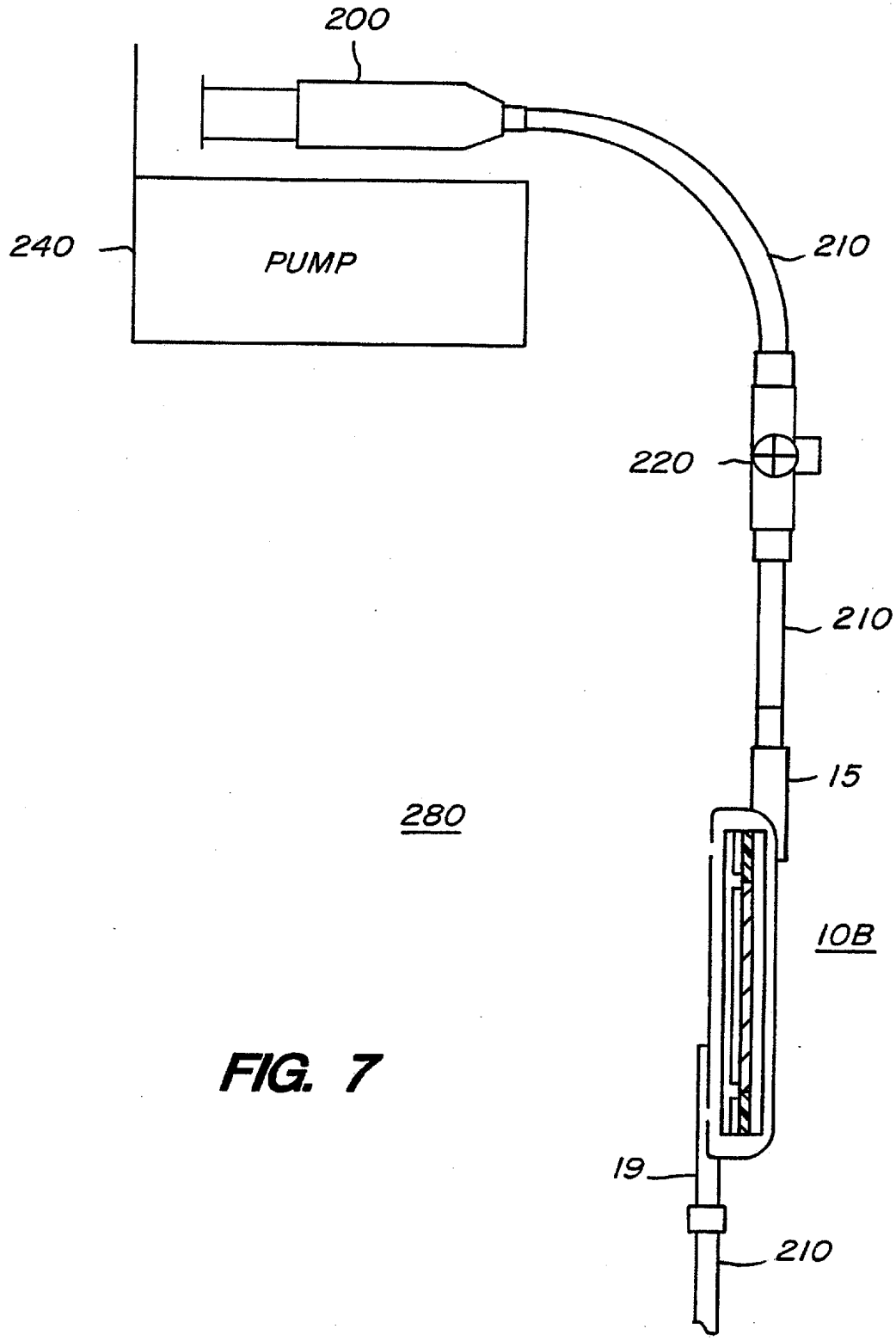


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04021

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :B01D 37/00, 27/00
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 210/436, 446, 472, 500.21, 502.1, 641, 650, 767; 55/159; 422/1, 101; 436/177; 604/4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,915,839 (Marinaccio et al.) 10 April 1990 See entire document	1-4, 6-10, 12-14
Y	US, A, 4,954,256 (Degen et al.) 4 September 1990 See entire document	5, 11, 15
Y,P	US, A, 5,126,054 (Matkovich) 30 June 1992 See entire document	5, 11, 15
A	US, A, 4,617,124 (Pall et al.) 14 October 1986 See entire document	1-4, 6-10, 12-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 JULY 1993	Date of mailing of the international search report 29 JUL 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer ROBERT A. DAWSON Telephone No. (703) 308-2340

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERN TIONAL SEARCH REPORT

International application No.
PCT/US93/04021

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

210/436, 446, 472, 500.21, 502.1, 641, 650, 767; 55/159;
422/1, 101; 436/177; 604/4

Form PCT/ISA/210 (extra sheet)(July 1992)*

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 94/02129
A61K 31/26, 9/16, 9/50	A1	(43) International Publication Date:	3 February 1994 (03.02.94)

(21) International Application Number: PCT/EP93/01739

(22) International Filing Date: 6 July 1993 (06.07.93)

(30) Priority data:
2228/92-6 15 July 1992 (15.07.92) CH

(71) Applicant *(for all designated States except US)*: CIBA-GEIGY AG [CH/CH]; Klybeckstrasse 141, CH-4002 Basle (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : LUKAS, Gerhard [DE/CH]; In den Wegscheiden 16, CH-4132 Muttenz (CH). RAMSTEIN, Henri [FR/FR]; Rue des Landes, F-68300 Rosenau (FR). KEMMETHMÜLLER, Hans, Stefan, J. [DE/DE]; Edith-Stein-Strasse 9, D-7800 Freiburg (DE). BÜSCHER, Gottfried [DE/CH]; Lohweg 8, CH-4054 Basle (CH).

(74) Common Representative: CIBA-GEIGY AG; Patentabteilung, Klybeckstrasse 141, CH-4002 Basle (CH).

(81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: VETERINARY MEDICINAL ANTHELMINTIC PREPARATION CONTAINING NITROSCANATE

(57) Abstract

The present invention relates to a veterinary medicinal anthelmintic preparation for oral administration to productive livestock or domestic animals, which preparation contains the compound 1-isothiocyanato-4-(4-nitrophenoxy)benzene known as nitroscanate, and is formulated as follows: active drug 0.5 to 90 %; with a particle size of 0.1 to 100 µm; solid carrier 0 to 98 %; with a particle size of 100 µm to 3 mm; surfactant 0.1 to 10 %; antifoam 0.5 to 20 %; suspension stabiliser/disintegrator 0 to 5 %; protective coating/binder 0.1 to 10 %; wetting agent 1 to 10 % and filler 0 to 50 %. The novel preparation has substantial advantages over known nitroscanate preparations.

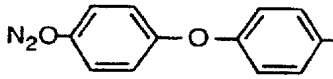
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**MR**	Mauritania
AU	Australia	**GA**	Gabon	**MW**	Malawi
BB	Barbados	**GB**	United Kingdom	**NE**	Niger
BE	Belgium	**GN**	Guinea	**NL**	Netherlands
BF	Burkina Faso	**GR**	Greece	**NO**	Norway
BG	Bulgaria	**HU**	Hungary	**NZ**	New Zealand
BJ	Benin	**IE**	Ireland	**PL**	Poland
BR	Brazil	**IT**	Italy	**PT**	Portugal
BY	Belarus	**JP**	Japan	**RO**	Romania
CA	Canada	**KP**	Democratic People's Republic of Korea	**RU**	Russian Federation
CF	Central African Republic			**SD**	Sudan
CG	Congo	**KR**	Republic of Korea	**SE**	Sweden
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovak Republic
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LU**	Luxembourg	**TD**	Chad
CS	Czechoslovakia	**LV**	Latvia	**TG**	Togo
CZ	Czech Republic	**MC**	Monaco	**UA**	Ukraine
DE	Germany	**MG**	Madagascar	**US**	United States of America
DK	Denmark	**ML**	Mali	**UZ**	Uzbekistan
ES	Spain	**MN**	Mongolia	**VN**	Viet Nam
FI	Finland				

VETERINARY MEDICINAL ANTHELMINTIC PREPARATION CONTAINING NITROSCANATE

The present invention relates to a veterinary medicinal anthelmintic preparation for oral administration to productive livestock or domestic animals, which preparation contains the compound 1-isothiocyanato-4-(4-nitrophenoxy)benzene known as nitroscanate and which, owing to its specific formulation, is effective in substantially lower concentration than the known anthelmintic preparations containing the identical active drug and, in addition, can now also be readily used as broad spectrum anthelmintic for controlling helminth infestations in all productive livestock and domestic animals, including cats.

The novel veterinary medicinal anthelmintic preparation contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) of formula  as active drug and is formulated as a granulate of the following composition, in which all percentages are by weight:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0	to	98 %;
with a particle size of	100 µm	to	3 mm;
surfactant	0.1	to	10 %;
antifoam	0.5	to	20 %;
suspension stabiliser/ disintegrator	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	1	to	10 % and
filler	0	to	50 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

The antifoam, the suspension stabiliser/disintegrator, the filler and the carrier may be identical substances, but they can have different functions within the formulation. The

filler may typically have the properties of binder or disintegrator.

The term "adjunct" used throughout this specification shall be understood as meaning all formulation components except the active drug. Some adjuncts may have different functions and therefore fall into different groups of adjunct.

Depending on the mode of preparation, the granular formulation of this invention may have different embodiments. Preferred embodiments typically include extruder granulates and fluidised bed granulates. These last mentioned granulates are especially preferred within the scope of this invention.

A preferred extruder granulate contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) as active drug and is in the form of a granular formulation of the following composition in which all precentages are by weight:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0		
surfactant	0.1	to	10 %;
disintegrator	0 %;		
suspension stabiliser/ disintegrator	0.5	to	20 %;
protective coating/binder	1	to	10 %;
wetting agent	1	to	5 % and
filler	0	to	50 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

One of the preferred fluidised bed granulates contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) as active drug and is in the form of a granular formulation of the following composition in which all percentages are by weight:

active drug	0.5	to	50 %;
with a particle size of	0.1	to	100 µm;
solid carrier	45	to	98 %;
with a particle size of	100 µm	to	3 mm;

surfactant	0.1	to	10 %;
suspension stabiliser/ disintegrator	0.01	to	1 %;
suspension stabiliser	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	0	to	2.5 %; and
filler	0	to	10 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

Within the scope of the novel anthelmintic granular formulations, fluidised bed granulates are especially preferred which vary from the above particulars in one or other of the following features:

active drug	0.5	to	20 %;
with a particle size of	1	to	20 µm;
solid carrier	80	to	98 %;
with a particle size of	100 µm	to	1.0 mm;
surfactant	0.1	to	1 %;
suspension stabiliser/ disintegrator	0.1	to	1 %;
suspension stabiliser	0.1	to	2 %;
protective coating/binder	0.1	to	5 %;
wetting agent	0.8	to	1.2 %; and
filler	0	to	10 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

1-Isothiocyanato-4-(4-nitrophenoxy)benzene known as nitroscanate is disclosed in DE-OS1 568 021 as a compound having anthelmintic properties. Its activity spectrum is thus known per se and embraces worms that are parasites of warm-blooded animals and are designated as helminths (nematodes, cestodes and trematodes). The target group specified in this publication comprises productive livestock and domestic animals, including cattle, pigs, horses, sheep, goats, dogs and cats. It is proposed to administer the drug in a single dose or repeatedly, the single dose being from 25-1000 mg/kg, depending on the species of animal.

Later, a number of scientific studies were published in which nitroscanate was administered for controlling worm species in different domestic animals, preferably dogs and cats.

In Research in Veterinary Science (1975) 19, 217-219, Gemmel et al. describe the effect of nitroscanate (10-20 µm) on *Echinococcus granulosus* and *Taenia hydatigena* infections. The drug was administered to the dogs in the form of capsules mixed with the feed. Successful results were obtained with dose rates of 250 mg/kg of bodyweight. At the same time, however, unacceptable side-effects such as vomiting, diarrhoea and tranquillising effects were also observed.

Two years later, the same authors again described in Research in Veterinary Science (1977) 22, 391-392 the effect of of nitroscanate (2-3 µm) on *Echinococcus granulosus* and *Taenia hydatigena* infections in dogs. In this case too the drug was administered to the dogs in the form of capsules. The authors recommended a single treatment of 64 mg/kg against *Echinococcus granulosus* and of 16 mg/kg against *Taenia hydatigena*. The authors again referred to undesirable side-effects such as vomiting.

In 1979, Gemmel et al. reported in Research in Veterinary Science (1979) 27, 255-257 on completely identical trials, except that the drug was this time administered to the dogs in tablet form. Depending on the worm species, statistically significant action was evidently achieved with single treatments of 32-250 mg/kg, whereas the efficiency of lower doses (2 mg/kg → 16 mg /kg) was statististically not significant. Here again the authors cited the earlier observed side-effects.

In the same year, Boray et al. reported in the Australian Veterinary Journal (1979) 55, 45-53 in their article "Nitroscanate a new broad spectrum anthelmintic against nematodes and cestodes of dogs and cats" on trials carried out with dogs and cats, and recommended the administration of nitroscanate at a dose rate of 25 to 200 mg/kg, depending on species of worm and host animal. These authors too reported on a number of undesirable side-effects, including vomiting, diarrhoea and loss of appetite.

It is therefore not entirely surprising that, in later publications, warnings on the use of nitroscanate are repeatedly found, especially as regards the use in cats, e.g:
R.K. Reinecke in 'Veterinary Helminthology' (Butterworths Durban/Pretoria) (1983),

page 169 "Never use nitroscanate in cats".
William C. Campbell and Robert S. Rew in 'Chemotherapy of Parasitic Diseases' (Plenum Press New York und London) (1986) Seite 413 "Nitroscanate is not recommended for the treatment of cats, as it has toxic side effects".
Trevor Turner in 'The Veterinary Record' August 8, 1987, 121, 121-123 declares on page 121 that Nitroscanat is "not suitable" for the treatment of cats.

The drug nitroscanate has been known to be an excellent broad spectrum anthelmintic but, as pointed out in the above dicsussion, there have been serious shortcomings of the dosage forms in which it has hitherto been administered and which have greatly restricted its use in veterinary practice.

The present invention has therefore for its object to provide a veterinary medicinal anthelmintic preparation in which the outstanding anthelmintic broad activity spectrum of nitroscanate is fully effective and which does not have the undesirable side-effects observed so far, and which can be used without problems for all productive livestock and domestic animals, including cats.

This object is achieved in surprisingly simple manner by the provision of the said novel preparation. It has now been found that an anthelmintic preparation containing nitroscanate and formulated as described at the outset in fact meets the required desiderata. The composition not only exhibits an activity in accord with the demands of practice, i.e. full activity against helminths in productive livestock and domestic animals in unusually low single doses of less than 25 (preferably 2 to 24) mg/kg, but also has a long shelf-life, a high acceptance in feed by the host animal, and is distinguished by the additional feature that the user virtually does not come in contact with the active drug owing to the protective film surrounding the particles. Furthermore, the administration of the novel preparation is extremely uncomplicated, as it is in granular form and can simply be mixed with the feed. In addition, the palatibility, i.e. the acceptance by the productive or domestic animal, is enhanced by the neutrally flavoured protective coating.

It is of course possible to add further active ingredients having the the same or different activity to the novel anthelmintic granular formulations conveniently for broadening the activity spectrum or for treating another disease. Thus it is possible to blend the novel preparations with other classes of anthelmintics, ectoparasiticides, growth promoters, fertility enhancing substances, vitamins, appetite stimulators or builders.

Suitable solid carriers for the novel anthelmintic granular formulations are the following carriers: very readily or readily water-soluble or water-dispersible crystalline carriers such as monovalent or polyvalent sugars, carbohydrates, inorganic salts and compounds, as well as polymers which are suitable for oral administration to a warm-blooded animal and have sufficient palatibility. Particularly suitable solid carriers are different sugars. Such suitable carrier materials are known in the art of vetinary galenics.

Within the scope of this invention, the term "sugar" will be understood as meaning all sugars that are in solid form at room temperature. These sugars may be selected from the class of the mono- and oligosaccharides such as mono-, di-, tri-, tetra- and pentasaccharides. In a preferred embodiment of the invention, the mono- and oligosaccharides are aldoses or ketoses. In a particularly preferred embodiment of the invention, the monosaccharides are aldopentoses, aldohexoses, ketopentoses or ketohexoses.
An aldopentose may typically be D-ribose, D-arabinose, D-xylose or D-lyxose; an aldohexose may typically be D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose or D-talose; a ketopentose may typically be D-ribulose or D-xylulose; a ketohexose may typically be D-psicose, D-fructose, D-sorbose or D-tagatose.
A disaccharide may typically be trehalose, maltose, isomaltose, cellobiose, gentibiose, saccharose or lactose. Saccharose is of very particular interest.
A trisaccharide may be exemplified by raffinose. Polysaccharides may typically be cellulose, starch, dextrans, glycogen, fructans, inulin, mannan, xylans and arabinans.

Suitable surfactants within the scope of this invention are neutral, amphoteric, cationic and anionic surfactants having a HLB value greater than 10 (HLB = hydrophilic-lipophilic balance). Particularly suitable surfactants include fatty acid glycerol polyglycol esters. Suitable surfactants are basically nonionic, cationic and/or anionic surfactants having good emulsifying, dispersing and wetting properties. Surfactants will also be understood as meaning mixtures of surfactants.
Suitable anionic surfactants may be so-called water-soluble soaps as well as water-soluble synthetic surfactants.

Suitable surfactants coming under the heading of "soaps" are the alkali metal salts, alkaline earth metal salts or the ammonium or substituted ammonium salts of higher

(C_{10}-C_{22})fatty acids, and also the sodium or potassium salts of oleic or stearic acid.

Frequently, however, so-called synthetic surfactants are used, preferably fatty sulfonates, fatty sulfates, sulfonated benzimidazole derivatives or alkylarylsulfonates.

The fatty sulfonates or sulfates are usually in the form of alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts and generally contain a C_8-C_{22}-alkyl radical which also includes the alkyl moiety of acyl radicals, e.g. the sodium or calcium salt of lignosulfonic acid, of dodecylsulfate, or of a mixture of fatty alcohol sulfates obtained from natural fatty acids. These compounds also comprise the salts of sulfated and sulfonated fatty alcohol/ethylene oxide adducts. The sulfonated benzimidazole derivatives preferably contain 2 sulfonic acid groups and one fatty acid radical containing about 8 to 22 carbon atoms. Examples of alkylarylsulfonates are the sodium, calcium or triethanolamine salts of dodecylbenzenesulfonic acid, dibutylnaphthalenesulfonic acid, or of a condensate of naphthalenesulfonic acid and formaldehyde. Also suitable are corresponding phosphates, e.g. salts of the phosphated adduct of p-nonylphenol with 4 to 14 moles of ethylene oxide; or phospholipids.

Non-ionic surfactants are preferably polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, or saturated or unsaturated fatty acids and alkylphenols, said derivatives containing 3 to 30 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenols. Further suitable non-ionic surfactants are the water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol and alkylpolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethylene glycol ether groups and 10 to 100 propylene glycol ether groups. These compounds usually contain 1 to 5 ethylene glycol units per propylene glycol unit.

Representative examples of non-ionic surfactants are nonylphenolpolyethoxyethanols, castor oil thioxilate, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethylene glycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyoxyethylene sorbitan, e.g. polyoxyethylene sorbitan trioleate, are also suitable non-ionic surfactants.

Cationic surfactants are preferably quaternary ammonium salts which contain, as N-substi-

tuent, at least one C_8-C_{22}alkyl radical and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl or hydroxy-lower alkyl radicals. The salts are preferably in the form of halides, methylsulfates or ethylsulfates, e.g. stearyltrimethylammonium chloride or benzyl bis(2-chloroethyl)ethylammonium bromide.

The surfactants customarily employed in the art of formulation are described e.g. in the following handbook:

"Mc Cutcheon's Detergents and Emulsifiers Annual", MC Publishing Corp., Ridgewood, NJ USA, 1988",

Antifoams which may suitably be used are typically silicone oils, polymethylsiloxanes, oleates or laurates. Suitable antifoams are described in the technical literature, inter alia in Dr. H. P. Fiedler: 'Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete' (Lexicon of adjuncts for Pharmacy, Cosmetics and Related Fields), 3rd edition, Editio Cantor, D-Aulendorf (1989). Especially preferred antifoams are polysiloxanes and, among these, methylpolysiloxane antifoams. Antifoams of this type are also termed 'Antifoam AF'.

Suspension stabilisers and disintegrators may typically be crosslinked alkali metal or alkaline earth metal salts of carboxymethyl cellulose, hydroxypropyl celluloses, polyvinyl pyrrolidone, preferably crosslinked polyvinyl pyrrolidone or polyethylene glycols.
A particularly preferred suspension stabiliser is microcrystalline cellulose.

Protective coatings and binders suitable for use in the practice of this invention are water-soluble film-formers such as cellulose ethers, water-soluble polymethacrylates and polyethylene glycols. Especially preferred binders are cellulose ethers. For the extruder granulates it is expedient to use macromolecular binders with good adhesive properties, typically hydroxypropyl celluloses, preferably hydroxypropylmethyl cellulose.

Suitable wetting agents are the polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, saturated or unsaturated fatty acids and alkyl phenols defined in the paragraph relating to surfactants. Particularly preferred wetting agents are, however, polyethylene glycols, most preferably polyethelene glycol 6000.

By normal temperature will be meant hereinafter a temperature in the range from 0 to

c. 50°C, preferably room temperature. The expression "elevated temperature" means a temperature above 50°C, especially a temperature above c. 55 to c. 100°C.

The component termed "filler" is used solely to adjust a specific final concentration. Basically all substances named as carriers may be used as filler, although, in contradistinction to the carrier, the particle size of the filler is not a critical parameter.

If it is desired to provide the novel granular formulation in the form of a fluidised bed granulate, it will be prepared by carrying out the following steps at normal temperature (c. 55-100°C, preferably 15-35°C, preferably at room temperature):

1. grinding nitroscanate to a particle size in the range from 0.1 to 100 µm;

2. converting the ground nitroscanate into a spray suspension by suspending it in a mixture of demineralised water, a suitable surfactant or mixture of surfactants, one or more than one film-former and one or more than one optional suspension stabiliser:

3. spraying a suitable solid carrier material at elevated temperature, typically in a fluidised bed dryer, with the spray suspension;

4. preparing a coating solution by mixing demineralised water and one or more than one film-former, with or without additional adjuncts;

5. coating a granular formulation obtainable in step 3 with a coating solution obtainable in step 4, conveniently in a fluidised bed dryer, at elevated temperature (c. 50-100°C, preferably 70-90°C);

6. isolating the dried and coated fluidised bed granular formulation.

If it is desired to provide the granular formulation in the form of an extruder granulate, it is prepared by carrying out the following steps at normal temperature (c. 0-50°C, preferably 15-35°C, preferably at room temperature):

1. grinding nitroscanate to a particle size in the range from 0.1 to 100 µm;

2. blending the finely ground nitroscanate with a disintegrator, a wetting agent and a

binder;

3. making the resultant mixture into a paste with a solution or dispersion of one or more than one surfactant in demineralised water;

4. extruding the moist paste to form cylindrical pellets through suitably dimensioned orifices, typically using rams or roll mills;

5. preparing a coating solution by mixing demineralised water and one or more than one film-formers, with or without additional adjuncts;

6. coating a granular formulation obtainable in step 4 with a coating solution obtainable in step 5, conveniently in a fluidised bed sprayer, at elevated temperature; and

7. isolating the dried and coated extruder granular formulation.

Preparation of the granulates

Example 1: Preparation of 2 kg of novel fluidised bed granulate

The drug nitroscanate is comminuted in a suitable grinding apparatus, most suitably an air jet mill. The grinding operation is controlled such that the desired particle size of 0.1 to 100 µm is attained. To prepare the spray suspension, 10.0 g of polyoxyethlated hydrogenated castor oil are dissolved in 700 g of demineralised water, then 20.0 g of polyethylene glycol 6000 are added, followed by the addition of 2.0 g of antifoam emulsion, and 200 g of the finely ground nitroscanate are suspended therein. A dispersing unit can be used for better dispersion of the ingredients. The supension is deaerated by applying a vacuum. With constant stirring, 20.0 g of microcrystalline cellulose are added, followed by the addition of 50.0 g of hydroxypropylmethyl cellulose. During this addition it is advantageous to prevent air from being stirred in. To prepare the coating solution, 50 g of hydroxypropylmethyl cellulose are stirred into 400 g of demineralised water and dissolved by stirring.

1648 g of sugar are charged to a fluidised bed sprayer and preheated to 50-80°C with warm air. After the desired temperature has been reached, the spray suspension is sprayed by a pump through a nozzle on to the fluidised carrier material. The flow of air is so

chosen that a uniform turbulent fluidised bed is obtained. Suitable nozzles are typically monofluid or two-fluid nozzles. Two-fluid nozzles are especially suitable. The optimum pumping rate and the further optimum machine parameters are each determined for the respective apparatus employed. A possible machine setting is:

air flow	$30m^3/h$
air flow temperature	60°C
exhaust air temperature	40°C

After application of the spray suspension, the coating solution is sprayed on to the particles in the same manner. After the spraying operation, the granulate is dried in a stream of warm air.

Example 2: Preparation of 2 kg of the novel extruder granulate

The drug nitroscanate is comminuted in a suitable grinding apparatus, most suitably an air jet mill. The grinding operation is controlled such that the desired particle size of 0.1 to 100 µm is attained.
180 g of the comminuted drug are thoroughly mixed with 70 g of microcrystalline cellulose, 50 g of hydroxypropylmethyl cellulose and 20 g of polyethylene glycol 6000. Mixing can conveniently be effected in a ploughshare mixer.

10 g of polyoxyethlated hydrogenated castor oil are dissolved in 460 g of demineralised water. The drug/adjunct mixture is wetted with the resultant solution. This wetted mixture is then passed through an extruder with a c.1 mm orifice. This operation can be repeated a number of times for further compaction of the granulate.

To prepare the coating solution, 50 g of hydroxypropylmethyl cellulose are stirred into 450 g of demineralised water and dissolved by stirring. The cylindrical pellets obtained by extrusion are preheated to a temperature of c.50-80°C in a fluidised bed apparatus with warm air. After the desired temperature has been reached, the coating solution is sprayed on to the fluidised extruder granulate through a nozzle under the conditions described in Example 1. Finally, the coated extruder granulate is dried, preferably in a stream of warm air.

Examples of novel fluidised bed granulates

Example G1:

nitroscanate (2-20 µm)	10.0 g
sugar	82.4 g
polyethylene glycol 6000 vet	1.0 g
hydrogenated castor oil, polyoxyethylated	0.5 g
methylpolysiloxane emulsion	0.1 g
microcrystalline cellulose	1.0 g
hydroxypropylmethyl cellulose	5.0 g

Example G2:

nitroscanate (2-20 µm)	10.0 g
lactose, crystalline	81.1 g
polyoxyethylated sorbitan laurate	0.7 g
methylpolysiloxane emulsion	0.2 g
microcrystalline cellulose	1.5 g
hydroxypropylmethyl cellulose	5.5 g

Examples of novel extruder granulates

Example G3:

nitroscanate (2-20 µm)	1 800.0 g
microcrystalline cellulose	70.0 g
hydroxypropylmethyl cellulose	100.0 g
polyethylene glycol 6000 vet	20.0 g
hydrogenated castor oil, polyoxyethylated	10.0 g

Biological Examples for determining efficiency and tolerance

Example B1: Treatment of cats naturally infected with Toxocara cati (roundworm of cats)

20 cats naturally infected with Toxocara cati were divided into 4 groups. The granulate was given to each group of 5 cats with the feed at dose rates of 15 mg/kg, 10 mg/kg or 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the cats. During the entire assay, the cats were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated cats was reduced by a specific percentage which was dose-dependent.

dose (mg/kg)	15	10	5
efficiency (%)	100	98	86

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B2: Treatment of cats artifically infected with Taenia taeniaeformis (tapeworm of cat)

35 cats artifically infected with Taenia taeniaeformis were divided into 4 groups. The granulate was given to each group of cats with the feed at dose rates of 15 mg/kg (4 cats), 10 mg/kg (9 cats) or 5 mg/kg (8 cats) of nitroscanate. 14 cats were untreated. After 5 days, a count was made of the number of worms that had survived the treatment. During the entire assay, the cats were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated cats was reduced by a specific percentage which was dose-dependent.

dose (mg/kg)	15	10	5
efficiency (%)	100	95	79

In the entire time after the treatment, no clinical symptoms were observed that would

indicate a side-effect of the treatment.

Example B3: Treatment of dogs naturally infected with several worm species (tapeworm, hookworm, roundworm)

15 dogs naturally infected with Taenia sp, Ancylostoma caninum and Toxocara canis were divided into 3 groups. The granulate was given to each group of 5 dogs with the feed at dose rates of 10 mg/kg or 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by a specific percentage which was dose-dependent.

Dose (mg/kg)	Efficiency (%)		
(Worm species ⇒)	Taenia	Ancylostoma	Toxocara
5	20	98	77
10	91	100	100

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B4: Treatment of dogs naturally infected with several worm species tapeworm, hookworm, roundworm)

15 dogs naturally infected with Taenia sp, Ancylostoma caninum and Toxocara canis were divided into 3 groups. The granulate was given to each group of 5 dogs with the feed at dose rates of 10 mg/kg or 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by a specific percentage which was dose-dependent.

Dose (mg/kg)	Efficiency (%)		
(Worm species ⇒)	Taenia	Ancylostoma	Toxocara
5	88	100	74
10	100	100	98

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B5: Treatment of dogs naturally infected with Ancylostoma caninum (dog hookworm)

10 dogs naturally infected with Ancylostoma caninum were divided into 2 groups. The granulate was given to each group of 5 dogs with the feed at a dose of 10 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by 93 %.

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B6: Treatment of dogs naturally infected with Dipylidium caninum (dog tapeworm)

10 dogs naturally infected with Dipylidium caninum were divided into 2 groups. The granulate was given to each group of 5 dogs with the feed at a dose of 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by 92 %.

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B7: Treatment of dogs naturally infected with Dipylidium caninum (dipyladiasis)

15 dogs naturally infected with Dipylidium caninum were divided into 2 groups. The granulate was given to a group of 4 dogs with the feed at a dose of 15 mg/kg of nitroscanate and 11 dogs were untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by 98 %.

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

What is claimed is:

1. A veterinary medicinal anthelmintic preparation which contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) as active drug, which preparation is formulated as a granulate and has the following composition:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0	to	98 %;
with a particle size of	100 µm	to	3 mm;
surfactant	0.1	to	10 %;
antifoam	0.5	to	20 %;
suspension stabiliser/ disintegrator	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	1	to	10 % and
filler	0	to	50 %,

such that all components together do not exceed 100 %.

2. A veterinary medicinal anthelmintic preparation according to claim 1 which is formulated as an extruder granulate and has the following composition:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0		
surfactant	0.1	to	10 %;
disintegrator	0 %;		
suspension stabiliser/ disintegrator	0.5	to	20 %;
protective coating/binder	1	to	10 %;
wetting agent	1	to	5 % and
filler	0	to	50 %,

such that all components together do not exceed 100 %.

3. A veterinary medicinal anthelmintic preparation according to claim 1 which is

formulated as a fluidised bed granulate and has the following composition:

active drug	0.5	to	50 %;
with a particle size of	0.1	to	100 µm;
solid carrier	45	to	98 %;
with a particle size of	100 µm	to	3 mm;
surfactant	0.1	to	10 %;
suspension stabiliser/ disintegrator	0.01	to	1 %;
suspension stabiliser	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	0	to	2.5 %; and
filler	0	to	10 %,

such that all components together do not exceed 100 %.

4. A veterinary medicinal anthelmintic preparation according to claim 3 which is formulated as a fluidised bed granulate and has the following composition:

active drug	0.5	to	20 %;
with a particle size of	1	to	20 µm;
solid carrier	80	to	98 %;
with a particle size of	100 µm	to	1.0 mm;
surfactant	0.1	to	1 %;
suspension stabiliser/ disintegrator	0.1	to	1 %;
suspension stabiliser	0.1	to	2 %;
protective coating/binder	0.1	to	5 %;
wetting agent	0.8	to	1.2 %; and
filler	0	to	10 %,

such that all components together do not exceed 100 %.

5. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) for the preparation of a granulate as claimed in any one of claims 1 to 4 for controlling helminths in productive livestock and domestic animals.

6. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 5

for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being an extruder granulate.

7. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 6 for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being an extruder granulate of the composition as indicated in claim 2.

8. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 5 for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being a fluidised bed granulate.

9. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 8 for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being a fluidised bed granulate of the composition as indicated in either claim 3 or claim 4.

10. Use of a granulate as claimed in any one of claims 1 to 4 for controlling helminths in productive livestock and domestic animals.

11. A process for the preparation of a granulate as claimed in claim 1 containing 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) for controlling helminths in productive livestock and domestic animals, which granulate is prepared in the form of (A) a fluidised bed granulate by carrying out the following steps at normal temperature:

1. grinding nitroscanate to a particle size in the range from 0.1 to 100 µm;
2. converting the ground nitroscanate into a spray suspension by suspending it in a mixture of demineralised water, a suitable surfactant or mixture of surfactants, one or more than one film-former and one or more than one optional suspension stabiliser:
3. spraying a suitable solid carrier material at elevated temperature, preferably in a fluidised bed sprayer, with the spray suspension;
4. preparing a coating solution by mixing demineralised water and one or more than one film-formers, with or without additional adjuncts;
5. coating a granular formulation obtainable in step 3 with a coating solution obtainable in step 4, preferably in a fluidised bed sprayer, at elevated temperature (c. 50-100°C, preferably 70-90°C);

6. isolating the dried and coated fluidised bed granulate;
and (B) as an extruder granulate by carrying out the following steps at normal temperature:
1. grinding nitroscanate to a particle size in the range from 0.1 to 100 µm;
2. blending the finely ground nitroscanate with a disintegrator, a wetting agent and a binder;
3. making the resultant mixture into a paste with a solution or dispersion of one or more than one surfactant in demineralised water;
4. extruding the moist paste to form cylindrical pellets through suitably dimensioned orifices;
5. preparing a coating solution by mixing demineralised water and one or more than one film-formers, with or without additional adjuncts;
6. coating a granular formulation obtainable in step 4 with a coating solution obtainable in step 5, preferably in a fluidised bed sprayer, at elevated temperature; and
7. isolating the dried and coated extruder granulate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01739

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/26; A61K9/16; A61K9/50

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	FR,A,1 491 477 (AGRIPAT S.A.) 11 August 1967 cited in the application see claim 1 see page 5,right column,lines 1-27	1-11
A	GB,A,2 224 933 (MERCK) 23 May 1990 see claims see page 5, line 31 - line 35 see page 6, line 10 - line 23 see page 7, line 22 - line 25	1-11

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 SEPTEMBER 1993	07. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01739

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4 117 156 (W.LOEWE) 26 September 1978 see claims see column 7, line 28 - line 40 see column 8, line 5 - line 19 see column 9, line 24 - line 32 see example 2	1-11
A	CHEMICAL ABSTRACTS, vol. 92, no. 8 Columbus, Ohio, US; abstract no. 64644v, cited in the application see abstract & RES.VET.SCI. vol. 27, no. 2, 1979, pages 255 - 257 M.A.GEMMEL ET AL. 'The effect of nitroscanate tablets on Echinococcus Granulosus and Taenia Hydatigena infections in dogs'	1-11

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301739
SA 76575

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 28/09/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-1491477		None		
GB-A-2224933	23-05-90	None		
US-A-4117156	26-09-78	AU-B-	508845	03-04-80
		AU-A-	1596176	19-01-78
		DE-A,C	2631524	03-02-77
		FR-A,B	2317920	11-02-77
		GB-A-	1541710	07-03-79
		JP-C-	1323455	27-06-86
		JP-A-	52012932	31-01-77
		JP-B-	60053007	22-11-85
		NL-A-	7607939	20-01-77
		OA-A-	5390	28-02-81

EPO FORM P0479